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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

APRIL, 1949

ORIGINAL ARTICLES

WHY ARE FEVER TEMPERATURES OVER 106° F. RARE?*

By Eugene F. DuBois, M.D.
NEW YORK, NEW YORK

(From the Department of Physiology, Cornell University Medical College, and the Russell Sage Institute of Pathology in affiliation with The New York Hospital)

There is difficulty in considering high temperature by itself because it is so closely associated with the symptoms of infection. As a rule the highest readings are found in the most severe stages of the worst fevers. They are accompanied by all the manifestations of toxemia acting upon a patient weakened by partial starvation.

High temperature in itself can damage tissues but it is hard to estimate the level at which each particular organ is injured. Exceptional patients have survived temperatures of 113° F. (45° C.) but there are not many who live more than a few days or weeks after the temperature has reached 107° F. (41.7° C.). We know from the work of fever therapists that persons in good condition can stand 107.6° F. (42° C.) for periods of 8 to 10 hours but this is close to the upper limit of tolerance. Temperatures within 2 degrees of this danger level are seldom found in fever. Why are readings of 106° F. rare?

The facts at our command can be best explained by assuming that the temperature regulating mechanism functions well at the higher thermostatic level set by the particular disease. There must be an emergency mechanism that strongly resists the approach to levels that threaten life.

Moderately high temperature around 104° F. (40° C.) cannot be regarded as dangerous or even deleterious, inasmuch as it is the level found in athletes during hard exercise. Muscles are most efficient at this temperature. Patients in good condition adjust themselves well to moderate fever. We noted this in the old days in Bellevue Hospital when there were still many typhoid patients. If they were able to take a well balanced, high-calory diet they were so clear mentally that with temperatures of 104° F. they sat propped up in bed reading the newspaper every morning.

There is still much to be learned about temperature regulation in health and even more to be learned about fever. We are quite ignorant regarding the details of the chemical, electrical and physical reactions which occur in the hypothalamus and skin in response to changes in temperature. It is by delicate adjustments in these tissues that the balance between heat loss and heat production is maintained. We know little about the causation of fever

* Thirty-first Mellon Lecture presented before the Society for Biological Research, School of Medicine, University of Pittsburgh, May 27, 1948.

and the manner in which fever producing substances affect the level of thermostatic control. A study of high fever may throw light on this control.

There is an extensive literature on temperature regulation reviewed by Thauer[9] and by Ranson and Magoun.[7,8] In a recent small monograph on fever, DuBois[3] has published 2 graphs indicating the limits of body temperature. The first gives the range found in normal persons with a lower limit of 96° F. (35° C.) for early morning in cold weather and an upper limit of

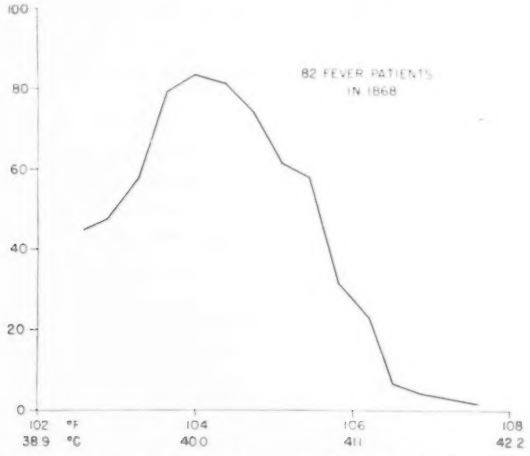

FIG. 1.—All the axillary temperature readings above 39° C. in the 82 fever charts in the appendix to Wunderlich's book on The Temperature in Diseases, 1871. The ordinates give the number of readings at each level of temperature.

104° F. (40° C.) for the rectal temperature of athletes after hard exercise. In the second graph he has tried to show the limits of human survival. The lower limit is about 74° F. (23° C.) and the upper about 113° F. (45° C.). Only a few persons have survived at these extremes. The safe upper limit of temperature for persons in good condition has been closely approached by the fever therapists when they deliberately maintain temperatures of 42° C. (107.6° F.) for 8 or even 10 hours.

Lee[6] in an excellent review of heat and cold has described the normal temperatures of homeotherms and the upper safe limits of body temperature. Most mammals have temperatures between 97 and 102° F. with upper safe limit of 107 to 110° F. Birds with more labile normal, 105 to 107° F., have an upper safe limit of 113° F. Lee speaks of the considerable species difference with little obvious evolutionary plan and no high correlation of normal with upper lethal body temperature.

In an article on body temperature prepared in 1939 DuBois[2] recorded the rectal temperature readings of 100 unselected patients in the medical wards of The New York Hospital. None was above 105° F. (40.5° C.) and none below 96.8° F. (36° C.). He suggested that there was a secondary regulation of temperature at about the level of 105 to 106° F. In a similar study made in 1948 it was obviously unfair to use the 1948 ward patients. The formerly well established fever courses of many diseases have been so distorted by sulfanilamides, penicillin and streptomycin that they are almost unrecognizable. It was therefore necessary to go back to the older literature and to the record of patients in the New York Hospital before 1932.

In making the analysis care was taken to omit all readings influenced by cold baths, cold sponges, serums or by intravenous injections that might have contained pyrogens. It was also necessary to omit all readings in the last 2 days of life because temperature regulation is seriously impaired in moribund patients. Cases of heat stroke were placed in a special category. Only readings above 39° C. (102.2° F.) were recorded.

One of the best studies of fever is the classical book of Wünderlich[10] published in 1868 and translated into English in 1871. The clinical thermometer had only just been introduced and there was so much enthusiasm for the new instrument that the physicians themselves made the readings. They measured axillary temperatures, which in high fevers are very close to rectal readings. Fortunately Wünderlich in the appendix to his book gives the charts of 82 patients with high fevers including typhoid, typhus, pneumonia, and the exanthemata. Fig. 1 charts all his readings above 39° C. (102.2° F.).

Similar graphs were made for 100 patients with lobar pneumonia and 100 with malaria admitted to the New York Hospital before 1932 (Fig. 2). Twenty-five patients were studied who had been given malarial fever therapy in the same hospital between 1932 and 1948. Inasmuch as relapsing fever has the reputation of giving the highest temperatures, the literature was searched and the readings in 50 cases of various types of this disease were recorded in a separate graph.

There was a marked similarity in the temperature distribution curves of these diseases of widely different etiology. The greatest number of readings, the peaks of the curves, came between 40.0° and 40.8° C. Temperatures above 106° F. (41.1° C.) were rare. This point was brought out even more clearly in Figures 3 and 4. In 1761 readings, only 75 were above 106° F. There must be an automatic cut-off that stops the rise of temperature before it reaches the level where high temperature itself becomes a menace to life.

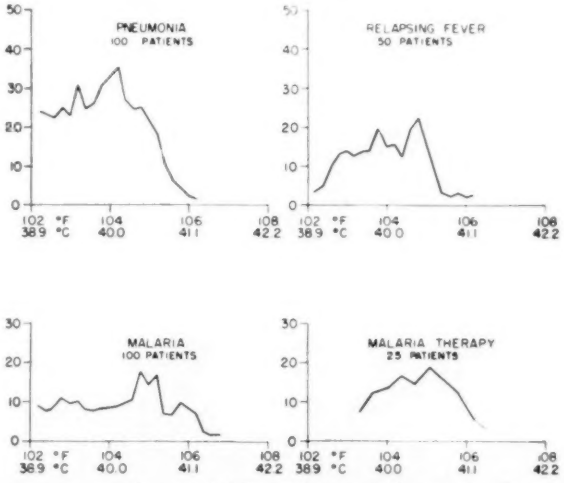

FIG. 2.--Rectal temperature readings in 4 different fevers. Ordinates give the number of readings at each level of temperature.

The fact that there were 608 readings between 104 and 105° F. (40.0°-40.6° C.) and less than half as many between 102 and 103° F. was unexpected. The shape of the curve indi-

cates that in these particular high fevers the thermostatic control was set in the neighborhood of 104 and 105° until defervescence was well established. Of course the shape of the curve would have been very different if the milder infections such as bronchitis, chicken pox and influenza had been included.

In examining the records it was obvious that there is a tendency to place the dot on the full degrees more often than on the nearest fractions. For example the number of recordings at 40.0° C. greatly exceeded those at 38.8 or 40.2°. Therefore the curves were smoothed by averaging with each column the readings of its right hand and left hand neighbors. It must also be realized that when measurements are made every 4 or even every 2 hours some of the highest and lowest points are missed. The sharp peaks and valleys of hospital temperature charts are artefacts. When we study fever patients in the Sage respiration calorimeter and make readings every 4 minutes with electrical thermometers the curves are smooth and rounded.

The respiration calorimeter has also brought out the fact that there is no one body temperature and that it is impossible to determine accurately an average body temperature. The highest temperature is found in the liver or in the muscles in the case of severe work. The rectal temperature averages about 1° F. below that of the liver, the oral temperature another degree lower. The skin and subcutaneous tissue may be 2 to 3° lower in a warm environment or more than 60° F. lower in a cold environment. About one-fifth of the body substance lies within 1 cm. of the surface and its temperature changes are best indicated by skin readings.

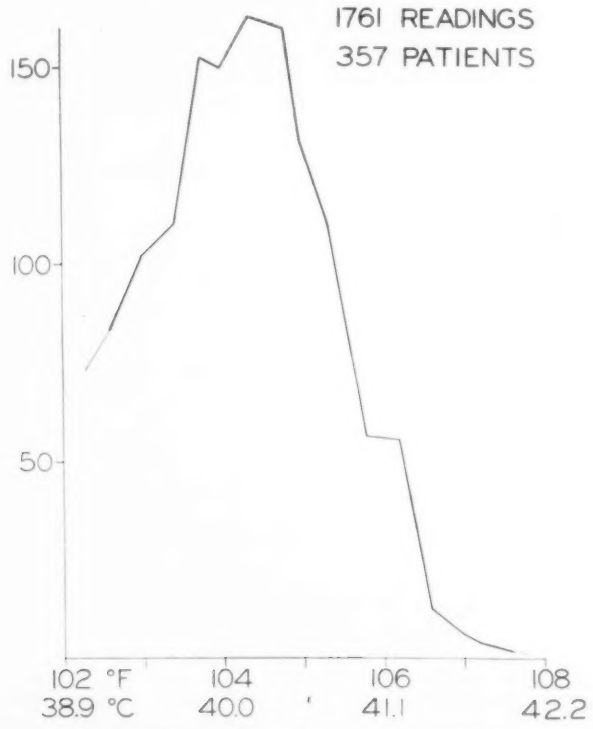

FIG. 3.—The readings of FIGS. 1 and 2 combined.

The rectal readings usually indicate the changes in about 80% of the body mass. These percentages vary with the environment and when the skin is really cold the gradient penetrates much deeper than a centimeter. Under these conditions the temperature changes of about one-half the body mass are best indicated by changes in skin temperature. At the other extreme, in fever, the blood is cooled near the surface and the subcutaneous temperature is close to the rectal.

During a chill with relative cooling of the surface and rapid rise of rectal temperature the superficial and internal masses of the body change at different rates and often in different directions. In severe exercise also the skin temperature falls while the rectal temperature rises. It is obvious that in some conditions heat may be transferred from one part of the body to another without significant alteration in the overall temperature of the body mass.

Bearing in mind these limitations we still have in the graphs a fairly accurate picture of the highest temperatures of the internal organs including the hypothalamus which most authorities believe to be the region of the temperature regulating mechanism. The question that concerns us now is the existence of a mechanism in febrile disease that prevents the body temperature from rising above 106° F.

Were it not for such a mechanism the body temperature could rise from 40 to 43° C. just as easily and rapidly as it rises from 37 to 40° C. There is no physical reason to prevent the body temperature from shooting up to 44° C. (111° F.) or higher. It only requires a storage of 60 calories to raise the average man's temperature 1 degree Centigrade. During a severe chill a man can store more than 200 calories an hour. With severe exercise an athlete can store this amount in a few minutes.

High body temperature is accompanied by an increase in basal metabolism and patients with fever temperatures of 40° C. exhibit heat productions of about 40% above the normal. This may be augmented by restlessness or even delirium. The rise is partially compensated by an increased radiation and convection as the temperature of

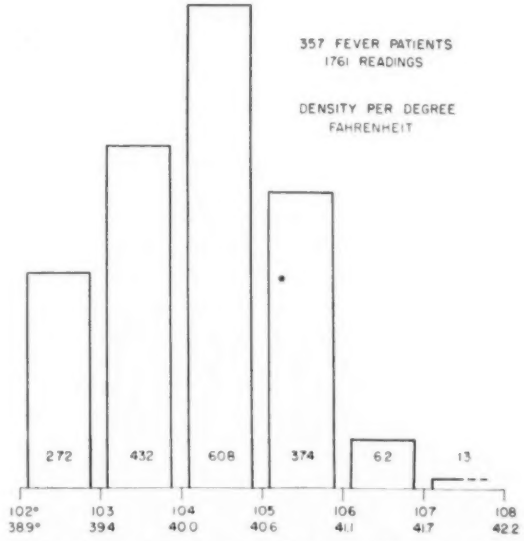

FIG. 4.—The readings of FIGS. 1 and 2 combined in a density chart per degree Fahrenheit.

the skin rises more and more above that of the environment. For example, if the temperature of the air and walls of the hospital ward be 20° C. (68° F.) and the patient's rectal temperature 40° C., skin temperature 38° C., there would be a gradient of 18° C. between skin and air. If his rectal temperature were 44° C. and skin temperature 42° the gradient would be 22° C. It is doubtful if this 4 degree difference is significant in comparison with the major channel of heat loss, vaporization. If it were important we would find fever temperatures 5 or 10 degrees higher on hot summer days than they are in winter.

There are several special conditions in which body temperatures do exceed 41° C. The best known is fever therapy. If the patient is put in a cabinet and heat loss through the skin prevented, the body temperature will rise progressively. If extra heat is poured into the body, temperatures will rise rapidly to any desired level. Occasionally it gets out of control and the rise continues after the patient has been removed from the fever cabinet.

A second well known cause of marked hyperthermia is heat stroke. No attempt will be made to review the extensive literature on this subject but attention is called to the excellent study of Ferris, Blankenhorn, Robinson and Cullen[4] who have described in great detail 44 cases of heat stroke in Cincinnati in the hot spell of 1936. Most of the patients were brought to the hospital after 3 days of intensely warm weather, few had been exposed to much direct sunlight. Those with admission temperatures over 106.8° F. were comatose or delirious. It so happened that all with temperatures under 107° F. (41.7° C.) ultimately survived and that a few with temperatures at the top of the clinical thermometer failed to die. Many of the patients reported that a few hours before they were prostrated they had noticed that sweating stopped. All of them on admission had hot, dry skins.

Several other reports of heat prostration have recorded that all of the skins were hot and dry. A few have described some patients with moist skins but these may have been cases of heat exhaustion which differs from heat stroke in that it resembles shock with failure of the peripheral circulation and with a normal or only slightly elevated temperature.

It is difficult to see how a man who can sweat normally could possibly develop heat stroke except in conditions of high humidity. Blum[1] estimates that soldiers marching in the desert increase their metabolism up to 265 calories an hour, 4 times the basal level, and in addition they may receive from the direct sunlight, reflected heat and hot air an additional load of over 200 calories an hour. They gain heat through radiation and convection and the only channel of loss is vaporization. This rises to adequate high levels. The men vaporize 1 to 1½ liters of water an hour and each liter vaporized takes care of about 585 calories. Similar results have been obtained in carefully controlled laboratory experiments. When, however, the humidity is high as it would be in a jungle, vaporization becomes less effective and under the stress of heavy work the internal temperature rises to 103° F. or higher until work becomes impossible.

If under long continued stress there is finally an exhaustion of the sweat glands the body temperature rises with great rapidity. A few studies of fatigue of sweat glands have been described by Lee[6], and by Gerking and Robinson[5] who observed a group of healthy, well acclimated soldiers walking on a treadmill in a hot room. They were kept in water and salt balance by drinking 0.1% saline solution. In the first 2 hours of work the average rate of sweating was 1400 gm. per hr. and the sweating rates declined from 10 to 80% of this

value by the 6th hour. They conclude that the sweating mechanism was fatigued though not exhausted. Apparently this is not often the result of dehydration or lack of salt. It is very different from the blockage of sweat glands by keratinization of their orifices as observed recently in the Pacific Area.

A third condition that exhibits temperatures above 106° F. (41.1° C.) is the moribund state a few hours before exitus. Usually in fevers the temperature mounts to high levels just before death. Sometimes it remains flat, sometimes it falls. In the last hours of life there is a failing of circulation and impairment of the temperature regulating mechanism.

A great deal has been written about abnormally high temperatures in brain injuries or tumors involving the hypothalamic region. From a limited study of many cases reported in the literature there is no evidence that the temperatures differ markedly from those found in infectious diseases. Probably the hyperthermias that have impressed clinicians are the terminal high temperatures of moribund patients.

Under certain special conditions it is possible to obtain very high temperatures in fever. If intravenous injections which happen to contain pyrogens are given to fever patients the results may be dramatic. I remember one such case when in 1921 at Bellevue Hospital Cecil and Larsen were treating lobar pneumonia with an antibody solution that caused a significant reduction in the mortality. In spite of every precaution known at that time an occasional batch would contain pyrogens. One poor patient after an intravenous injection had such a violent chill that the clinical thermometer rose to 110° F. and burst. The laboratory thermometer showed that his rectal temperature was 112° F. (44.4° C.). Prompt application of cold water reduced the fever rapidly and much to our surprise the patient recovered.

Summarizing these special conditions in which temperatures over 106° F. (41.1° C.) are found, the following classification can be made: (1) A sudden overwhelming heat load, as in a fever cabinet or the chill from pyrogens. (2) A prolonged overwhelming load with exhaustion of the sweat glands as in heat stroke. (3) Failure of the circulation and, or, failure of the temperature regulating mechanism in moribund patients. (4) Some infectious diseases with occasional readings between 41 and 42° C. These represent the scatter which is usually found at the edges of bell-shaped Gaussian curves of distribution.

Thus it is evident that in fevers the great majority of readings are lower than 106° F. which is safely below the point at which temperature itself is dangerous. Everything points to a temperature regulating mechanism that functions well at the thermostatic level set by the particular stage of the disease. Presumably this is located in the same centers in the hypothalamus that control temperature in health and respond grossly to changes in the blood and more delicately to changes in the skin. The sharp limitation of temperatures at the level of about 106° F. points toward an "emergency regulatory mechanism in fever" that protects the body with great efficiency.

This mechanism can do but little in the way of reducing heat production unless it sends the patient into a quiet coma. It cannot do much through increased radiation or convection but can do a great deal by increased peripheral circulation and particularly by increased sweating.

The patient can help if he is strong enough to throw off his blankets. The nurse can cool the room. The doctor can follow the custom of aiding nature's vaporization by ordering cool sponges with water or dilute alcohol. The important thing is to cool as much blood as possible in the subcutaneous

tissues. Too great a chilling of the skin might lead to constriction of the peripheral blood vessels and diminished cooling of the internal organs. There is also the possibility that chilling of the skin might start signals to the temperature regulating center that would produce an effect exactly the opposite of that which was desired.

Drinking cool water is comforting but relatively inefficient in reducing temperature. For example if a patient could possibly swallow a liter of water at zero Centigrade it would abstract 40 calories, enough to lower his temperature only 2/3 degree. This same water vaporized from his skin would abstract 585 calories.

Summary and Conclusions. 1. A survey has been made of 1761 temperature readings in 357 patients suffering from diseases characterized by high fever. Only 4.3% of the temperatures were above 106° F. (41.1° C.). None was above 107.8° F. (42° C.).

2. In these particular fevers 608 readings came between 104 and 105° F. (40.0 to 40.6° C.). Less than half as many fell between 102 and 103° F. (38.9 to 39.4° C.). These are indications that in these fevers the "thermostat level" for the temperature regulating mechanism was set in the neighborhood of 104 to 105° F.

3. Human temperatures much higher than 106° F. can be found in several conditions other than infectious diseases. The normal temperature regulating mechanism may be overwhelmed suddenly by a fever cabinet or gradually by heat stroke with its exhaustion of the sweat glands. The mechanism together with the peripheral circulation often fails in moribund patients.

4. Except for these anomalous conditions temperatures are kept safely below the danger level by an "emergency regulatory mechanism in fever" which acts chiefly through the peripheral circulation and the sweat glands.

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MAJOR SURGICAL OPERATIONS IN THE PRESENCE OF BUNDLE BRANCH BLOCK

A STUDY OF THE OPERATIVE RISK IN 59 PATIENTS

By Paul H. Pfeiffer, M.D.*

AND

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Tabulations of the operative mortality, cardiac complications and other postoperative complications in 59 patients with bundle branch block (BBB) subjected to major surgical operations at Memorial Hospital suggest that such patients withstand operation almost as well as patients of the same age group who have normal electrocardiograms. The presence of BBB has been regarded by some as a contraindication to the performance of all but emergency surgical procedures because of the danger of ventricular standstill or ventricular fibrillation.[4] This attitude is encouraged by studies stating that the average life expectancy associated with this electrocardiographic finding is 2 years.[3,6] A more recent survey, however, has shown that 42% of the 50 cases of BBB were still living 8 years and 2 months after the condition had been diagnosed.[1]

Bundle branch block in the aged is almost always associated with arteriosclerotic heart disease, although it may occur with rheumatic, syphilitic or congenital forms of heart disease. Any elderly patient who must undergo major surgery should have a careful preoperative evaluation of his cardio-vascular status; but our data do not support the contention that BBB *per se* constitutes a major contraindication to surgery. Other factors, such as the presence of cardiac hypertrophy, congestive failure, a history of recent myocardial infarct appear to us to be of far more importance than the presence of a single electrocardiographic abnormality. All these criteria must be evaluated if the internist is to give an intelligent estimation of the operative risk. Increasing knowledge of pre- and postoperative care, perfected techniques of anesthesia, and the introduction of antibiotics have combined to make the prognosis for patients with heart disease undergoing major surgery much less formidable.

Cancer is invariably a fatal disease in the absence of treatment and, moreover, its course in the untreated patient is often harrowing. For this reason surgical treatment of cancer patients may be given more liberally than in most diseases. Emphasis must be placed, however, on employing every possible means to insure recovery of the patient with cardiovascular disease who must undergo surgery for the ablation of cancer. This line of procedure has became a cornerstone in the treatment of patients with cancer at Memorial Hospital, and consequently we have been able to collect a rather large series of patients with BBB who have had major surgical operations during a 27 month hospital period.

In this communication the authors have attempted to answer the following questions: (1) Do patients with bundle branch block undergoing surgical procedures have an unusually high imme-

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diate mortality? (2) Does the surgical procedure cause an acceleration or an aggravation of the cardiac disease as manifested clinically or by electrocardiographic tracings? and (3) Do patients with BBB have an unusually high incidence of postoperative complications?

Method of Study. Fifty-nine patients with BBB were subjected to major surgical operations at Memorial Hospital from March 1, 1946, to June 1, 1948. During the same period, 13,716 patients were admitted and 4,891 electrocardiograms were made—the incidence of BBB being 1.88% of the electrocardiograms made and 0.66% of the hospital admissions. These figures were not corrected for repeated electrocardiograms or readmissions.

We define a major operation as any procedure lasting 1 hour or longer, whether or not a general anesthetic agent was used. The data were analyzed for age, sex, and race incidence. The charts were reviewed and insofar as possible an effort was made to classify the heart disease according to the New York Association Classification. The cardiovascular background was evaluated by noting a history of, or findings of, rheumatic fever, syphilis, hypertension, myocardial infarction, cardiac enlargement or congestive failure. Preoperative management, including the use of digitalis and quinidine; the type, length and course of operative procedure, the anesthesia employed and the postoperative course and care were reviewed. The incidence and variety of postoperative complications were noted with special emphasis being placed upon a search for those which might have some etiological relation to the presence of heart disease. Bundle branch block was classified according to accepted criteria.[2] The S wave pattern was considered separately, since there is some evidence that it is associated with a better prognosis.[5,7]

TABLE 1.—ESSENTIAL DATA ACCORDING TO TYPES OF BUNDLE BRANCH BLOCK

		Total Number of Cases (59)	L B B B (18)	A L B B B (12)	R B B B (1)	S Wave (28)
N. Y. Heart Association Classification*	Class I A and B	51	16	11	1	23
	Class II A and B	8	2	1	0	5
Past History (Cardiac)	Infarct	5	2	2	0	1
	Angina	4	2	0	0	2
	Congestive Failure	8	1	2	1	4
Diastolic Blood Pressure above 90 mm.		29	12	2	0	15
	No X-ray	6	3	2	0	1
X-ray Evidence of Cardiac Enlargement	None	39	8	8	0	23
	Slight	8	5	1	1	1
	Moderate	2	0	1	0	1
	Marked	4	2	0	0	2
Post-operative non-fatal medical complications		10	4	1	1	4
Post-operative deaths		6				
	Surgical	3	3	0	0	0
	Medical	3	0	0	0	3
Patients who have survived 19 months or more		10	0	1	0	9

* There were no cases in Classes III and IV.
L B B B B—Left bundle branch block.
A L B B B—Atypical left bundle branch block.
R B B B—Right bundle branch block.
S Wave—Atypical right bundle branch block.

Preoperative Evaluation. In Table 1 are summarized the essential data of

the preoperative study, the postoperative complications, deaths and prolonged survivals according to the type of bundle branch block found. There were 30 left bundle branch blocks (LBBB), of which 18 were typical and 12 were atypical. There were 29 right BBBs, of which 1 was typical and 28 were of the S wave type. The average age was 66.6 years with the following distribution: 1 was between 41 and 50 years, 9 were between 51 and 60, 30 between 61 and 70, 18 were 71 to 80 and 1 was between 81 and 90 years of age. There were 41 males and 18 females; 3 patients were colored, 2 males and 1 female; all others were white. In 1 case there was clinical evidence of rheumatic heart disease; in the others, there being no evidence of rheumatic, luetic or congenital heart disease, the etiology of the BBB was probably arteriosclerotic. A diastolic pressure of 90 mm. of mercury or above was present in 29 or 49% of the patients. The pulse pressures were distributed as follows: 9 were between 31 and 40; 10 between 41 and 50; 11 between 51 and 60; 6, 61 to 70; 9, 71 to 80; 9, 81 to 90; and 5 between 91 and 100. A preoperative

TABLE 2.—TYPES OF ANESTHESIA AND OPERATIONS PERFORMED

Type of Operation	No.	Ether	Spinal	Pentothal	Novocaine
Total Laryngectomy	6			4 (1)	2
Radical Neck Dissection	6			6 (1)	
Abdomino-perineal Resection	6	2	4 (2)		
Uretero-intestinal Transplant	5	4 (1)	1 (1)		
Cystectomy	4	1 (1)	3 (1)		
Sigmoid Resection	3	1	2		
Subtotal Gastrectomy	3	2		1	
Radical Mastectomy	4	2		2	
Lobectomy (right upper lobe)	2	2 (1)			
Exploratory Laparotomy	2	1	1 (1)		
Thyroidectomy (one with radical neck dissection)	2	1		1 (1)	
Transurethral Resection	2	1	1		
Total Gastrectomy	1	1			
Transthoracic Cardiectomy	1	1 (1)			
Splenectomy	1	1			
Hysterectomy	1				1
Cholecystectomy	1	1			
Exploratory Thoracotomy	1	1			
Radical Groin Dissection	1				1
Axillary Dissection	1	1			
Perineal Resection	1	1			
Resection of Maxilla	1			1	
Appendectomy	1		1		
Partial Laryngectomy	1			1	
Partial Cystectomy	1	1			
Simple Mastectomy	1	1			
Cervical Rhizotomy	1	1			
Partial Glossectomy	1	1 (1)			
Transverse Colostomy	1	1			
Excision of Vagina	1	1			
Excision Basal Cell Tumor	1			1	
Excision, Carcinoma of Ear	1			1	
Excision of Buccal Mucosa	1			1	
Excision of Sarcoma of Chin	1			1	
Excision of Parotid Tumor	1			1	
Suprapubic Cystotomy	1		1		
TOTAL	69	30	14	21	4

The figures in parenthesis indicate cases with a fall in diastolic pressure to 50 mm. of mercury or below.

diastolic pressure below 60 mm. of mercury was not observed. All patients had a preoperative hemoglobin of at least 75% (photoelectric)—the standard being 15.5 gm. for males and 14.4 gm. for females. Six patients had a fasting blood sugar of 120 mg. per 100 cc. or more. The blood urea nitrogen was within normal limits in all patients prior to the operation. One patient had clinical evidence of polycythemia. Preoperative medications included the continuance of maintenance doses of digitalis in the 6 patients who were receiving it when they came to the hospital; and, in addition, 4 patients were given therapeutic doses of digitalis and quinidine preoperatively as a prophylactic measure. There was roentgenological evidence of slight, moderate or marked cardiac enlargement in 14 of the 53 cases in which 6 foot chest films were available. The criteria used were: (1) for slight enlargement, the transverse diameter of the heart exceeded one-half the internal diameter of the chest by 1 to 2 cm. (2) for moderate enlargement, by 3 to 4 cm. and (3) for marked enlargement by 5 or more cm.

TABLE 3.—NON-FATAL MEDICAL AND SURGICAL POSTOPERATIVE COMPLICATIONS

Medical	No. of Cases	Surgical	No. of Cases
Bronchopneumonia	3	Urinary Incontinence	2
Atelectasis	2	Wound Abscess	2
Paralytic Ileus	2	Wound Slough	2
Thrombophlebitis	1	Pneumothorax	2
Pulmonary Embolus	1	Wound Dehiscence	1
Tachycardia (? type)	1	Intestinal Obstruction (due to adhesions)	1
		Acute Urinary Retention	1
		Esophageal Fistula	1
		Chyle Fistula	1
		Hematoma	1
TOTAL	10	TOTAL	14

Operative and Postoperative Course. In Table 2 the operations and anesthetic agents are listed. In 13 cases there was a drop in diastolic pressure to 50 mm. of mercury or below. The pressure remained at dangerous levels in 2 cases for 1 hour—in all others it was rapidly (within 5 to 20 minutes) restored to normal by neosynephrine subcutaneously or by whole blood transfusions. Six of the 12 cases developing significant hypotension received ether, 3, spinal, and 3, pentothal anesthesia. There were 69 major operative procedures performed on these 59 patients. Seventeen of the operations lasted between 1 and 2 hours, 18 between 2 and 3 hours, 23 lasted 3 to 4 hours, and 11 lasted 4 to 5 hours. In no instance was an operation terminated because of a serious complication arising on the operating table.

As for the postoperative period, there were 6 patients who died from 3 to 19 days after the operation; these will be discussed in more detail below. Parenteral fluids were administered to 8 of the 59 patients as hypodermoclyses —an unusually high incidence since fluids are almost never given subcutaneously in this hospital. There were 10 patients who received 1500 cc. a day of normal saline intravenously for 1 to 4 days and only 1 developed signs of congestive failure. He died on the 16th postoperative day in pulmonary edema after having received large amounts of blood, plasma, saline and 50% glucose by vein; he was found at post-mortem examination to have a recent occlusion of the right coronary artery. Only 2 patients manifested evident cyanosis

during the postoperative period and they, as well as 8 others, received oxygen either by tent or nasal tube. There were 4 patients whose hemoglobin dropped to below 65% after the operation—the lowest being 48%. A transient azotemia with elevation of the blood urea nitrogen from 20 to 44 mg. per 100 cc. was noted in 9 cases. In addition, all but one of the 6 patients who died had significant azotemia. The patients with diabetes were kept under good control and the patient with polycythemia did not suffer any unusual complications. In Table 3 the non-fatal medical and surgical postoperative complications have been listed. The average hospital stay was 19.8 days. No correlation was noted between the type or severity of the complications and the form of BBB or the preoperative evaluation.

Autopsy Findings. Post-mortem examinations were performed on 7 of these patients, 6 of them having died within 19 days of the operation and 1 died 3 months later. Evidence of myocardial infarction was found in 2 cases; 1 with LBBB and the other with the S wave pattern. The other hearts showed atherosclerosis of the coronary vessels with resultant myocardial fibrosis. The weights of all but one of the hearts were obtained, as follows: 285, 400, 410, 420, 430, and 530 gm. In 3 cases the cause of death, generalized peritonitis and massive hemorrhage, was regarded as surgical; in the other 3 the causes of death were: coronary thrombosis, pulmonary embolus, and bronchopneumonia with acute pyelonephritis.

Results. In Table 4 the follow-up studies on 59 patients with BBB who underwent major operations are presented. There was an immediate postoperative (within 19 days) mortality of 10%; one-half of these were classified as medical deaths. Eight patients have since succumbed to recurrent or metastatic malignant disease which makes it impossible to evaluate what the longevity of these patients would be if the BBB alone were considered. In only 5 cases was there evidence of progression of the heart disease following the operation. One died at home, ostensibly of a coronary thrombosis 8 months after the operation, 2 patients were digitalized after 5 and 8 months, 1 developed angina after 4 months and 1 an unexplained tachycardia after 3 weeks. Ten patients survived 19 to 28 months without any symptoms of heart disease. All but one of these had the S wave type of BBB.

TABLE 4.—END RESULTS AT DIFFERENT POSTOPERATIVE PERIODS

	Postoperative					
	3–19 days	3 weeks–3 months	4–6 months	7-12 months	13–18 months	19–28 months
Immediate postoperative deaths	6					
Surgical	3					
Medical	3					
Deaths from Carcinoma			2	1	3	2
Death, cause not determined			1			
Deaths from heart disease and patients who had increasing cardiac symptoms		1 (tachycardia)	1 (digitalized)	1 (died ? coronary)		
			1 (angina)	1 (digitalized)		
Surviving patients without symptoms due to heart disease		9	5	11	6	8

Postoperative electrocardiograms were available in 21 cases and showed insignificant changes in 7 instances as follows: (1) reduction in rate from 71 to 50; (2) change of the QRS conduction time from 0.12 sec. to 0.11 sec.; (3) reduction in amplitude of the T waves 18 months after the operation and 6 months before death from pulmonary metastases; (4) inversion of TCF4; (5) the development of a high TCF4; (6) the appearance of periods of 2-1 auriculo-ventricular block, and (7) the appearance of numerous auricular and ventricular premature beats (2 cases).

sure, the cardiac size, the non-fatal medical complications, the postoperative deaths and the number of patients who survived 19 months or more after their operations. Study of this table fails to show any significant correlation between the type of BBB and the presence or absence of any of the factors just listed. In other words, there was no significant difference relatable to the type of BBB in the distribution of the number of patients with cardio-vascular symptoms; the number of patients with a history of angina, infarction or congestive failure; the presence of hypertension or cardiac

TABLE 5.—ELECTROCARDIOGRAPHIC DATA ACCORDING TO THE TYPE OF BUNDLE BRANCH BLOCK OBSERVED

	L B B B No. of patients 18	A L B B B No. of patients 12	R B B B No. of patients 1	S Wave No. of patients 28
P-R interval (sec.)				
.12-.20	16	12	1	23
.21-.23	0	0	0	2
.24-.26	1	0	0	0
Not determinable*	1 (idio-ventricular)			3 (Auricular fibrillation)
QRS interval (sec.)				
.12-.13	13	11	1	22
.14-.15	5	1	0	6
Q-T interval (sec.)				
.31-.40	12	10	1	21
.41-.43	2	0	0	4
.44-.48	3	2	0	3
.49-.50	1	0	0	0
Axis				
Normal	4	2	0	7
Left	14	10	0	15
Right	0	0	1	6

* 3 had auricular fibrillation; 1 had idio-ventricular rhythm.
Four patients with the S wave or R B B B finding had significant Q waves in the limb or precordial leads.

Electrocardiographic Findings. To recapitulate, 59 patients with bundle branch block were studied; of these 18 had typical left bundle branch block; 12, atypical left bundle branch block; 1 typical right bundle branch block; and 28 atypical, or S wave, right bundle branch block. In Table 1 the type of BBB is presented with respect to the classification of the type of heart disease and the cardiac past history, the diastolic blood pres-

enlargement; the incidence of medical complications; or the number of deaths due to medical complications. We are forced to conclude that the type of BBB in this series bore no relation to the extent of heart disease preoperatively or to the operative or postoperative course. A later follow-up may give interesting data on the survival rate, without recurrence of cancer, in the various groupings. The period of postoperative observation is not yet

long enough to permit conclusions as to the significance of the 19 to 28 months survival of 9 patients with S wave BBB as against only 1 survival of another type of BBB (atypical left).

No conclusions can be drawn from the mortality in this series, since there were but 6 deaths; we can merely state that the 3 patients succumbing to strictly surgical complications had left BBB and that the 3 dying from medical complications had right BBB of the S wave type. Five patients developed increasing cardiac symptoms postoperatively, 2 had LBBB, none had RBBB, 2 had S wave RBBB, and 1 atypical LBBB.

Table 5 gives the PR, QRS and QT times, the axis deviation and the various types of arrhythmia observed in the 4 types of BBB. The distribution of prolonged PR, QT, and QRS times is not significant according to the type of BBB; but of the whole group, 3 patients had PR intervals that were above normal; in 12 patients the QRS deviation was greater than 0.13 sec.; and in 15 the QT interval was above normal for the heart rate. Left axis deviation was seen in 24 patients with LBBB and in 15 with the S wave type of RBBB.

Discussion. Although it was not possible to get a comparable series of patients of the same average age (66.6 years) as the patients studied, we were able to obtain the operative mortality statistics on patients 60 to 71 years of age who underwent sub-total gastric resections, abdominal perineal resections and radical neck dissections for carcinoma at Memorial Hospital. The operative mortality for 32 patients who had sub-total gastric resections in this age group was 12.5%; for 64 patients who had abdominal perineal resections it was 3.3%; and for 164 patients who underwent radical neck dissection 2.3%, giving an average of 3.4% for the 260 patients.

The immediate postoperative mortality of the series of 59 patients with bundle branch block was 10% (6 deaths). However, 3 deaths were unrelated to the presence of heart disease, generalized peritonitis being responsible in 2 instances and uncontrollable hemorrhage in 1. One patient died from acute pyelonephritis following ureteral transplants to the bowel but was shown to have bronchopneumonia as a contributory cause of death at autopsy. If this patient is included as a medical death related to the presence of heart disease, the "medical" postoperative mortality is 5%; if this death is excluded it is 3.3%, indicating that the presence of bundle branch alone was of questionable importance in evaluating the operative risk in these 59 patients.

Only 3 patients developed symptoms and signs of congestive heart failure postoperatively, easily controlled in 2 instances and associated with fatal infarction in 1 patient. The incidence of medical and surgical postoperative complications was not excessive. Finally, it was observed that increasing cardiac symptoms occurred in 5 patients several weeks to months following discharge from the hospital.

Although the data demonstrate that the presence of bundle branch block does not by itself constitute a contraindication to major surgical procedures today, there is an increased risk in such patients which can be kept at a minimum by meticulous medical management. Preoperative care, the choice of anesthesia, and careful postoperative management have made it possible to treat surgical problems in such patients. The careful supervision of fluid and salt intake, the judicious use of digitalis, diuretics and oxygen and the wide availability of potent antibiotics facilitate the medical management of such patients; close cooperation between the surgeon and the internist is of the utmost importance.

Emphasis must be placed upon an adequate evaluation of the medical history, cardiac classification and physical findings rather than upon electrocardiographic evidence of bundle branch block. This electrocardiographic abnormality, in the absence of contraindications uncovered by careful medical consultation, should not influence either the surgeon or the internist in deciding upon the surgical management of the patient with cancer. Both may have reasonable expectations that the patient will survive the operation and that his heart disease will not be accentuated as a result of surgery.

The cardiac status of a patient is neither more nor less important than evaluation of the pulmonary, renal, neurological, metabolic or hormonal functions and over-emphasis of any one aspect of a medical or surgical problem may lead to disaster. It is of interest that of all patients with bundle branch block seen during the period of time covered by this study, only 3 were thought to be too poor as operative risks to withstand even palliative surgery.

The fact that none of our patients could be classified as having heart disease more severe than Class II B undoubtedly accounts, in part, for the relatively low operative mortality among the 59 patients studied. A greater mortality would be expected among patients with bundle branch block whose heart disease was classified as Class III or IV.

Clinical Summaries of the 6 Cases Who Died Within 19 Days of the Operation. CASE 1. J. R., a 76 year old white male, entered the hospital on 12/20/46, complaining of painless hematuria of 1 year's duration. Four years ago he had had an episode of acute left-sided heart failure thought to be due to a myocardial infarction. Physical examination revealed a fairly well-developed elderly male who weighed 142 lbs. and had a blood pressure of 160/120. The heart appeared to be slightly enlarged to the left. There was normal sinus rhythm and no evidence of heart failure. The electrocardiogram showed an S wave type of RBBB. The heart was found to be at the upper limits of normal size on Roentgen-ray examination. A suprapubic cystotomy was performed, lasting 1 hour under spinal anesthesia. The blood pressure dropped to 110/70 but responded rapidly to the subcutaneous injection of 3 minims of 1:1000 neo-synephrine. Postoperatively the hemoglobin was 78% of normal and the blood urea nitrogen rose from 18 to 23 mg. per 100 cc. The urinary output was poor. The patient became irrational, was put in an oxygen tent and given several hypodermoclyses containing saline. He died on the 16th postoperative day (1/14/47) in pulmonary edema.

At post-mortem examination the heart was found to weigh 530 gm. There was complete obliteration of the right coronary artery and a large old infarct with aneurysm formation involving the left ventricle.

CASE 2. A. T., a 75 year old white female entered the hospital on 6/30/47, complaining of epigastric distress of 1 year's duration. She had been slightly dyspneic for 1 year and thought that she was hypertensive. She was found to be well-nourished, weighed 159 lbs., and her blood pressure was 170/90. The heart appeared to be slightly enlarged to the left and there was a grade II, blowing systolic murmur at the apex. The lungs were clear and there was no ankle edema. The heart appeared slightly enlarged to the left on Roentgen-ray examination. The electrocardiogram showed an LBBB. The hemoglobin was 100% of normal. She received digitalis and quinidine before the operation as a prophylactic measure. A total gastrectomy was performed with ether and curare anesthesia. The operation lasted 3½ hours. The blood pressure fell briefly to 110/70. After the operation the temperature rose to 104° and 105° in spite of antibiotics. The patient died on the 14th postoperative day (7/27/47).

At post-mortem examination the heart was found to weigh 430 gm. The coronary arteries were patent. There was no evidence of cardiac failure. A leaking suture line had resulted in generalized peritonitis.

CASE 3. F. G., a 64 year old white male entered the hospital on 5/31/46 complaining of epigastric distress, anorexia and a 45 lb. weight loss during the previous 6 months. He was found to be fairly well-nourished and to weigh 178 lbs. The blood pressure was 110/70, the anteroposterior diameter of the chest was increased, and the breath sounds were distant. The electrocardiogram showed the S wave type of right bundle branch block. Roentgen-ray examination showed the heart was not enlarged. The preoperative hemoglobin was 100% of normal. A transthoracic

cardiectomy which lasted 5 hours was performed using ether anesthesia. The blood pressure fell to 96/60 for 10 minutes during the operation. An electrocardiogram taken after the operation showed inversion of T_3 and depression of QRS in the precordial leads. Except for an occasional rise in temperature to 101° the patient appeared to be doing well. He died suddenly on the 10th postoperative day (6/20/46).

At post-mortem examination a pulmonary infarct of the left upper lobe was found. The heart weighed 420 gm. There was no evidence of myocardial infarction.

CASE 4. L. E., a 74 year old white male entered the hospital for the first time on 2/3/47 complaining of intermittent hematuria of 6 months' duration. The past history was non-contributory. The patient was found to be a poorly nourished elderly male with a blood pressure of 130/80. There were a few coarse rhonchi throughout both lung fields. The heart was not enlarged to percussion and there was no ankle edema. The preoperative hemogoblin was 99% of normal. An electrocardiogram showed the S wave type of RBBB. Rontgen-ray examination showed the heart was not enlarged. The patient underwent an uneventful transurethral prostatectomy under spinal anesthesia. One month later he returned to the hospital in the same general condition and a bilateral uretero-intestinal transplant was performed. The operation lasted 3 hours. The blood pressure was 60/20 for 1 hour, and the patient received a total of 11 minims of 1:1000 neosynephrine subcutaneously. During the postoperative period the patient's pulse ranged from 130 to 140 and the temperature rose to 102. He received 8 cc. (1.6 mg.) of Cedilanid on the 2nd postoperative day. He died on the 3rd postoperative day (3/8/47).

At post-mortem examination acute pyelonephritis and bronchopneumonia were found. The heart weighed 410 gm. There was moderate atherosclerosis of the coronary vessels.

CASE 5. M. B., a 70 year old white female entered the hospital on 12/10/46 complaining of constipation and generalized abdominal cramps of 4 months' duration. The past history was non-contributory. She was well-nourished and the blood pressure was 150/96. The heart and lungs were normal. An electrocardiogram showed an LBBB. Roentgen-ray examination showed the heart was not enlarged. The hemoglobin was 95% and fasting blood sugars were 100 and 109 mg. per 100 cc. before the operation. An exploratory laparotomy and transverse colostomy were performed with spinal anesthesia. The operation lasted 1½ hours. The blood pressure dropped from 120/80 to 80/60 for 10 minutes and she twice received 3 minims of 1:1000 neo-synephrine subcutaneously. Following the operation the patient received insulin according to the pre-meal urine specimen as well as intravenously with infusions of dextrose and water. On 2 occasions she complained of weakness and sweating. Shortly after one of these episodes the blood sugar was found to be 74 mg. per 100 cc. She also complained of precordial pain radiating down the left arm. An electrocardiogram showed no significant change from the preoperative tracing. The patient received 1.2 mg. of digitoxin intravenously on the 2nd postoperative day. She died 12/19/46.

At post-mortem examination fecal contamination of the peritoneum due to leakage around the stoma was found. There was atelectasis of both lower lobes. The heart was said to be slightly hypertrophied but its weight was not recorded. There was moderate sclerosis of the coronary vessels but no thrombosis was observed.

CASE 6. H. H., a 59 year old white machinist entered the hospital on 2/20/48 complaining of pyuria of 6 months' duration. The past history was non-contributory. Physical examination revealed a well-developed, well-nourished male who weighed 171 lbs. The blood pressure was 160/70. The heart and lungs were normal; there were no signs of congestive heart failure. The preoperative hemoglobin was 92% of normal. The electrocardiogram showed an LBBB; and the heart was observed to be slightly enlarged on Roentgen-ray examination. Eleven days after admission a left uretero-intestinal transplantation was performed with ether anesthesia. The operation lasted 2½ hours and was uneventful. Two days after the operation the temperature rose to 101 and signs of atelectasis were noted. The signs subsided rapidly, and 15 days after the operation the patient was returned to the operating room where a cystectomy, right nephrectomy and prostatectomy, were performed with ether anesthesia. The procedure lasted 5 hours, the patient received 2500 cc. of whole blood and the blood pressure did not fall below 100/60. Immediately following the operation the patient was noted to be cold and sweaty and the blood pressure dropped to 110/70 from 130/90. An electrocardiogram showed no change and a blood transfusion gave prompt relief. The day after the operation signs of atelectasis were noted which responded to intratracheal aspirations. He was also digitalized as a prophylactic measure at this time. On the 8th postoperative day bilateral calf tenderness and pain in the left chest developed, whereupon intravenous heparin was administered for 5 days with good response. Six days after the last dose of heparin the patient began to bleed profusely from

the suprapubic wound; and, in spite of careful packing and blood transfusions he died on the following day (4/6/48), 19 days after the 2nd operation.

At post-mortem examination the heart was found to weigh 400 gm. There was no evidence of edema, consolidation or infarction in the lungs. There was a fistulous communication between the ileum and the pelvic cavity. The cause of death was a massive hemorrhage at the operative site in the suprapubic area, the exact source of which could not be determined.

Summary and Conclusion. 1. Fifty-nine patients (average age 66.6 years) with bundle branch block were subjected to major surgical operations. Two patients died 10 and 16 days postoperatively of medical complications, a 3.3% operative mortality to which the presence of heart disease presumably contributed. The total operative mortality, including strictly surgical complications, was 10%.

2. The operative mortality in 280 patients 60 to 71 years of age subjected to total gastrectomy (32 patients), abdominal perineal resection (64 patients) and radical neck dissection (164 patients) was 12.5%, 3.3% and 2.3% respectively, an average mortality for the 3 operations of 3.4%.

3. The presence of bundle branch block *per se* does not constitute a contraindication to surgical intervention. Careful classification of the heart disease and study of the functioning of other systems are of greater importance in evaluating operative risk.

4. Postoperative complications did not appear to be more frequent or more severe than might be expected for a comparable group of patients in the same age group.

5. No significant correlations could be demonstrated between the electrocardiographic and the clinical findings. The stress on the circulation imposed by the surgical procedure apparently did not aggravate the course of the heart disease.

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THE EFFECT OF ROENTGEN RADIATION ON THE PRODUCTION OF THORACIC DUCT LYMPHOCYTES*

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It has been widely recognized that lymphoid tissue is among the most sensitive indicators of damage by Roentgen radiation. Further, after large doses of radiation the blood lymphocytes disappear very rapidly from the peripheral blood and are virtually completely absent in 24 hours or somewhat less after the radiation is administered. It is the purpose of this report to record the changes in the numbers of thoracic duct lymphocytes and rate of flow of thoracic duct lymph in cats receiving a large, single dose of whole body Roentgen radiation.

Procedures. Thoracic duct cannulations were performed in 9 normal animals receiving no Roentgen irradiation and in 11 animals who were to receive 1500 r whole body irradiation. Lymph was collected in hourly or 2-hourly volumes in a graduated centrifuge tube and was prevented from clotting by the addition of 3 drops of 1% sodium heparin to the collecting container. After mixing, the lymphocyte count per c. mm. was determined in duplicate, the specimen volume recorded, and the total lymphocytes in the specimen computed. In each instance the values for the first 2 hours were designated as a baseline and expressed as 100%. The values for each succeeding specimen were then expressed as a ratio or percentage of the baseline. The first group of animals received no irradiation; the second group were irradiated after baseline values were determined.

The whole body irradiation in the amount of 1500 r uniformly results in the death of cats within 4 to 7 days. It is far in excess of the amount required to accomplish virtually complete disappearance of lymphocytes from the peripheral blood in 24 hours or less. The following factors were kept constant: Total dosage, 1500 r; K.V.P., 250; Milliamperage, 15; Target distance to center of cat, 22″; Filter, Aluminum parabolic + ½ mm. of copper; Half value layer, 2.15 mm. copper; Average rate of administration, 25 r per minute.

Presentation of data. It is not valid under the experimental procedure employed to estimate the changes in thoracic duct lymphocytes and in lymph flow purely on the basis of a comparison of values obtained before and after irradiation. It has been the experience of this laboratory that as a result of the procedure itself there is over a period of several hours some diminution in the rate of lymph flow, the total lymphocytes per unit of time, and, to a much lesser extent, of the numbers of lymphocytes per c. mm. of lymph. This occurs whether the animal is irradiated or not. It is therefore necessary to compare irradiated animals with non-irradiated animals that have been submitted to the same experimental procedure if valid conclusions are to be drawn.

The data are presented graphically in Figure 1. In the control group data are available for only 6 hours after the baseline.

Analysis and discussion of data. It can be seen that following 1500 r whole body irradiation, the lymphocyte count per c. mm. and the total lym-

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phocytes per unit of time in thoracic duct lymph of cats rapidly become depressed when comparison is made with determinations in normal animals subjected to cannulation. This is apparent within 2 hours after the beginning of irradiation and has become very marked after 6 hours. The changes in lymph volume suggest some reduction in lymph flow in the irradiated group, but with the relatively small number of animals on which data are available this may not be significant. The figures given are mean values, and, in the case of the irradiated group, are weighted somewhat high by the inclusion of a single animal whose behavior differed inexplicably from the remainder of the group. In this animal the total lymphocytes and lymphocytes per cu. mm. did not progressively fall in number but after a preliminary reduction actually remained relatively stationary for several hours after irradiation. This animal was followed for a considerable period of time, and eventually, some 12 hours after irradiation was begun, the counts fell to low values. It is well to include such exceptions to the general pattern of behavior after irradiation in order to illustrate the marked individual variation in the response of experimental subjects to radiation injury. However, in 6 animals the total lymphocytes were less than 15% of baseline values 6 hours after irradiation, while 8 hours after radiation was given this factor had fallen to less than 10% of baseline in 6 animals. In 3 animals the lymphocyte count per c. mm. of lymph was less than 6% of the baseline 8 hours after irradiation.

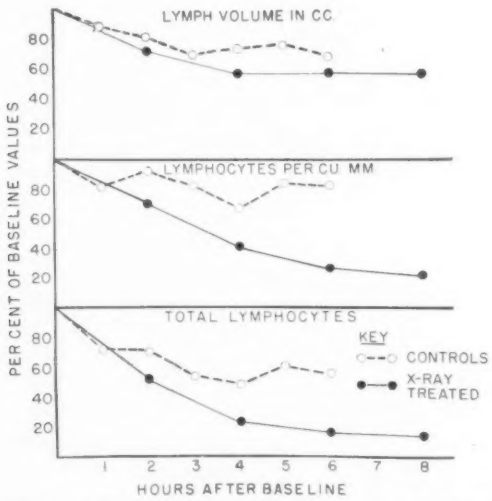

Fig. 1.—The mean values of normal and irradiated groups of cats are compared as regards lymph volume, lymphocytes per c.mm., and total lymphocytes per unit of time. In every instance the values for each specimen were expressed in each animal as a percentage of the baseline determination in the same animal, and then these percentages averaged for the group. In the irradiated group 1500 r whole body irradiation was begun at "O" hour and completed in about 1 hour. The studies were made on thoracic duct lymph.

There is rather strong reason to believe that mature leukocytes are detectably damaged only by tremendous doses of Roentgen radiation (much larger than those given here), and that it is the precursor cells which are so very sensitive to penetrating radiations. It is, of course, not possible to say that mature cells subjected to radi-

ation may not be destroyed at a rate more rapid than normal despite the apparent lack of morphologic damage. It does seem likely, however, that fully matured lymphocytes present in the lymphoid tissue at the time of irradiation can be expected later to appear undamaged in considerable numbers in the lymph draining those tissues. If such is the case the lymphocytes found in the thoracic duct lymph following 1500 r whole body irradiations are: (1) the progeny of cells still capable of undergoing mitosis for one or more times after irradiation (2) lymphocytes which were relatively mature at the time of irradiation and which were subsequently washed out morphologically intact by the flow of lymph through the nodes. In short, the joint phenomena of production plus release from storage account for the continued presence of lymphocytes in thoracic duct lymph for a time after heavy irradiation.

It is a fact that in these experiments the irradiated group of cats were able to produce in the first 8 hours after irradiation a total of only 104% of the number of lymphocytes produced in the 2 hours before irradiation. At the end of this 8-hour period the numbers of lymphocytes present were so small as to be almost negligible and were continuing to be reduced further. In addition, if the first 2 hours after the start of irradiation are disregarded, the animals were able to release in the subsequent 6 hours only 51.7% of the numbers of lymphocytes released during the 2-hour pre-irradiation period. Not all of this reduction in lymphocyte numbers can be attributed to the effects of irradiation. Part of it is artifact in that it results from the experimental technique since normal, untreated animals in control groups produced only 7/12 as many lymphocytes during a 6-hour period as would be anticipated from the baseline determinations. Using the reciprocal of this value, 12/7, we can correct to a reasonable degree the values obtained in the irradiated group.

When this is done we find a "corrected" value of 178% of the number of lymphocytes produced in a 2-hour pre-irradiation period released in the 8 hours after irradiation. Again neglecting the first 2 hours after the start of irradiation, the "corrected" figure for the subsequent 6 hours is 88.6% of the total lymphocytes produced in the baseline period. At the end of this time lymphocyte release was nearly at a standstill. Stated otherwise, if lymphocyte release subsequent to the 8th hour after irradiation is disregarded as negligible, the sum total of combined production plus release of mature cells from the lymphocyte warehouses after 1500 r whole body irradiation is begun amounts to somewhat less than a normal 4-hour supply. Moreover, within 2 hours after the start of irradiation, a potential of a little less than 2 hours' normal supply of lymphocytes remains in the nodes drained by the thoracic duct. If mature lymphocytes are not damaged severely by Roentgen radiation of this degree, then a reserve stock of less than 4 hours' normal supply is present within the lymph nodes; if all the lymphocytes released resulted from continuing production (as is highly unlikely), then no more than a 3 to 4 hour supply could be produced from the time irradiation was begun. If the former conditions are assumed the mature lymphocyte reserve is small indeed, while in any event production must cease or nearly cease quite promptly after severe radiation injury.

The above release of lymphocytes into the thoracic duct after 1500 r whole body irradiation can be employed to compute capacity for replenishment of the peripheral blood. If we assume our average cat to weigh 3 kg. the average blood volume (on a 5% of body weight basis) to be 150 cc.,

the average leukocyte count to be 15,000 per c.mm., and 25% of the cells to be lymphocytes, one can readily compute the average absolute lymphocytes to be 562.5 x 10^6. The number of the total number of circulating lymphocytes to be 562.5 x 10^6. The number of lymphocytes released in the 8 hours subsequent to the start of irradiation, even when "corrected" for the experimental procedure, could not exceed 314.8 x 10^6. Therefore, if the small number released after the 8th hour is disregarded, enough lymphocytes sufficient to replace slightly more than one-half the circulating lymphocytes are found in thoracic duct lymph after the amount of irradiation employed in these experiments. The computations admittedly lack strict quantitative accuracy, but it should be possible to rely on the order of magnitude of the changes observed.

Conclusions. The sum reserve of lymphocytes in the lymphoid tissues drained by the thoracic duct in cats is very small. From the time 1500 r whole body irradiation is *begun*, the total number of lymphocytes subsequently appearing in thoracic duct lymph amounts to no more than approximately a normal 4 hours' supply. Following this amount of Roentgen irradiation the numbers of lymphocytes in thoracic duct lymph very rapidly decrease, the reduction being noted within a very short time after irradiation is begun.

CONGENITAL HEMOLYTIC JAUNDICE IN A NEGRO FAMILY

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Congenital hemolytic jaundice is considered to be extremely rare in the Negro race. Wintrobe[7] encountered only one instance in a Negress of mixed blood. Scherer and Cecil[5] reported another case in a 14 year old Negress, and stated that in their rather extensive experience with Negro blood, this was the first case they ever noted. They also quoted Kracke and Haden as never having encountered any. Stragnell and Smith[6] observed three examples of this disease among 5 Negro siblings. In reviewing the records of the Presbyterian Hospital (New York), where Negroes constitute approximately 10% of the patients, these authors found 78 examples of congenital hemolytic jaundice in white, but only 1 in a mulatto woman. Goodman and Cates[2] studied another Negro family which included 3 sisters suffering from congenital jaundice. The only other possible instance in the literature is that of Merskey and Baskind[4] in an African native. This case had all the features of congenital jaundice, but because the family could not be studied, the authors were not able to rule out the possibility of its being acquired.

In the present report we wish to add three more cases of congenital hemolytic jaundice in a Negro mother and 2 daughters.

Case Reports. Case 1. M. R. W., mother, age 38, was first observed in another hospital where, in November, 1944, she was treated for pneumonia and latent syphilis (Wassermann 4+, Kline 4+). At that time she was discovered to have anemia with hemoglobin of 58% and red cell count of 2.28 million, but no special studies were made to determine the type of anemia.

She was readmitted to the same hospital 6 months later (May, 1945) by ambulance, in a semi-comatose condition. Previous to this admission she had complained of increasing weakness, abdominal pains and inability to do her housework. These symptoms became progressively worse until she lapsed into stupor. On admission, the blood pressure was 110/70, pulse imperceptible. The eyeballs were yellow and the mucous membranes very pale. There was evidence of pneumonia posteriorly on the right. Roentgenograph of the chest showed also enlargement of the heart, mainly to the right. The liver was palpable and tender. No mention was made of the size of the spleen.

Laboratory examination showed 1+ albumin and some red cells in the urine. Admission hemoglobin was 15%, red cell count 830,000 with 3.9% reticulocytes. Platelet, white cell count and differential were within normal limits. The red cells exhibited slightly increased fragility to hypotonic solution of saline, with hemolysis beginning at 0.47% and completed at 0.34%. Icterus index was 10. Sternal aspiration showed normal marrow with myeloid–erythroid ratio of 4 to 1. Wassermann reaction was 2+, Kline 4+.

The patient was treated with blood transfusions, the first 2 of which were accompanied by reactions. She was discharged approximately 1 month later with hemoglobin of 48%.

She was admitted to the Barnert Memorial Hospital nearly 3 years later, on April 19, 1948. In the interim she had been reasonably well, and bore one child, her seventh, without complications. Nine days previous to the present admission, the patient delivered a female infant, her eighth child, at home, spontaneously and without any immediate difficulties. However, on her third postpartum day, she developed generalized abdominal pain with vomiting and fever. After a few days the pain localized in the right upper

quadrant and right costovertebral area. The urine became darker in color and sclerae turned slightly yellow.

On examination the patient had typical Negroid features and dark brown skin. Temperature was 99.4°. The skull was "tower-shaped" (Fig. 1A), the sclerae slightly jaundiced, the mucous membranes very pale. There was a blowing systolic murmur at the apex. Roentgen-ray of the chest revealed moderate enlargement of the heart, mostly to the right. The liver extended approximately 2 fingerbreadths below the right costal margin and the firm tip of the spleen could be definitely felt on inspiration. The uterus was well involuted. There was no evidence of recent or old ulcerations of the legs.

FIG. 1.—A—Case 1. B—Case 2. Tower-shaped skull, more marked in A.

Laboratory examination showed severe anemia with marked spherocytosis and reticulocytosis, increased fragility of red cells and markedly increased excretion of urobilinogen in the urine (Table 1). The latter gradually decreased from 1:1200 to 1:40 (method of Wallace and Diamond), but even before discharge, 10 days later, she still excreted 380 mg. of urobilinogen in 24-hour stool specimen. Test for hemolysins in serum was negative. There was some evidence of temporary liver disturbance; cholesterol ester was reduced to 50% of total, and the albumin: globulin ratio was reversed, 2.3/3.5; cephalin-cholesterol flocculation test showed a 3+ reaction shortly after admission, but became negative on the day of discharge. Serological tests for syphilis gave the following results: Mazzini 4+, Kahn 1+, Kolmer ±. Roentgen-ray of the skull showed considerable thickening of the calvarium with widening of the diploic space, and some distortion in the outline of the clinoid processes of the sella turcica (Fig. 2A).

Therapy consisted solely of high protein diet. Transfusions were withheld because of the fear of reactions. The patient improved gradually, her temperature remained normal, and she was discharged with a hemoglobin of 7 gm. Splenectomy was refused.

As of last examination (June, 1948), she was asymptomatic except for slight yellow tint of the sclerae. The spleen was not palpable and hemoglobin was 9 gm.

CASE 2. A. R., age 9, daughter of M. R. W. (Case 1). This child was admitted to another hospital at the age of 6 years in May, 1945. Her illness coincided with that of her mother (see above) and manifested itself with similar symptoms, mainly, progressive weakness, epigastric distress and jaundice of one week's duration. Except for usual childhood diseases, she was apparently well until the onset of the present illness. Her temperature at the time of admission was 104°. The mucous membranes were very pale and the conjunctivae jaundiced. On Roentgen-ray examination, there was moderate enlargement of the heart, mostly to the right. The liver was 2 fingers and the spleen 1 finger below the costal margins.

Laboratory studies showed a hemoglobin of 22%, red cell count less than 2 million, reticulocytes 5%, increased fragility of red cells (beginning hemolysis of 0.50% saline, complete in 0.38%), icterus index of 14, and negative Kline test.

She remained in the hospital for 3 months running a febrile course. The spleen increased in size, then gradually decreased, and the fever abated. Therapy consisted of iron, liver extract and blood transfusions. Splenectomy was suggested but refused. She was discharged with a hemoglobin of 45% and red cell count of 3.0 million.

On examination at the Barnert Memorial Hospital clinic, in June, 1948, the child presented no complaints. She had been comparatively well for the past 3 years. She was

rather small for her age, but otherwise fairly well developed. Her skin was dark brown, the skull "tower-shaped" though less distinctly so than that of her mother's. (Fig. 1B). The sclerae were slightly jaundiced. The spleen could not be palpated. Roentgenograph of the skull revealed marked thickening of the Table 1). Aside from manifestations of her pulmonary condition, clinical examination was essentially negative. The spleen could not be palpated, though it appeared to be enlarged on Roentgen-ray films. Roentgenogram of the skull revealed no significant changes.

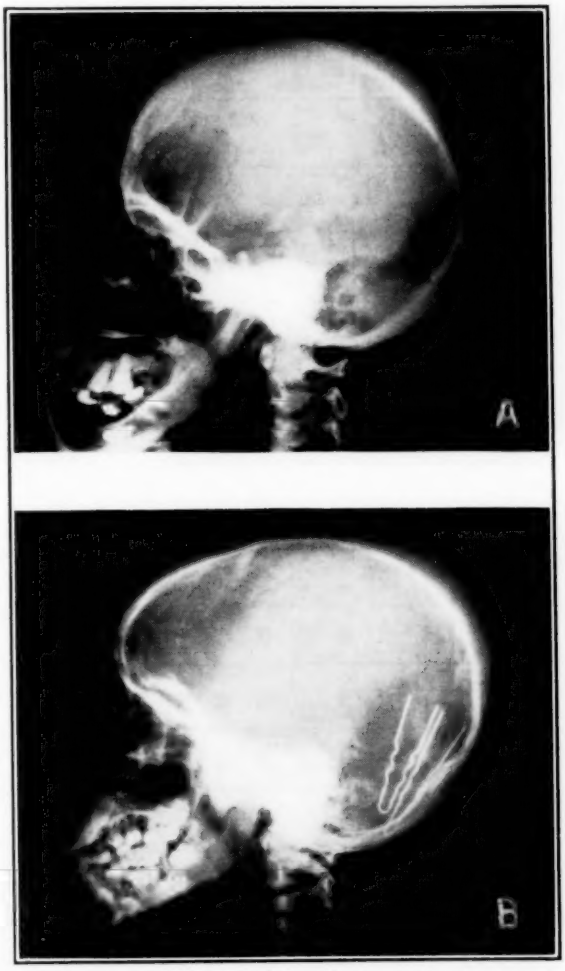

FIG. 2.—A—Case 1. B—Case 2. Thickening of the calvarium and widening of the diploic space.

frontal and parietal bones with widening of the diploic space and partial absorption of the outer table (Fig. 2B). The laboratory data are summarized in Table 1.

CASE 3. Do. R., age 5 daughter of M. R. W. (Case 1). For the past year and a half, this child has been treated in a sanatorium for adult type of pulmonary tuberculosis and was known to be anemic (hemoglobin 45%). Detailed study of the blood revealed changes typical of congenital hemolytic jaundice (see

STUDY OF THE FAMILY. In addition to the 3 members described above, the family consisted of 4 other children by the first husband (who had died of tuberculosis), and 2 more children by a second husband. None of these 6 children had congenital hemolytic jaundice, though all of them were slightly or moderately anemic, probably be-

Table .

Clinical Hematologic Data in 10 Members of a Negro Family, 3 of whom have Hemolytic Jaundice.

Name	Relationship	Age (Years)	Splenomegaly	Jaundice	Hemoglobin Gm. per 100 cc.	Red Blood Cells Million/cu. mm.	Hematocrit (Per cent)	Mean corpuscular hemoglobin ($\delta\ \delta$)	Mean corpuscular volume (cu. μ)	Mean corpuscular diameter (μ)	Mean corpuscular thickness (μ)	Spherocytes (Per cent)	Reticulocytes (Per cent)	Fragility of Red Cells		Sickling	Icterus Index	Urinary urobilinogen	Remarks
														Beginning hemolysis	Complete hemolysis				
M.R.W.	Pt.	37	+	+	6.5	2.6	19	25	72	6.4	2.25	20	14	.64	.40	0	20	Incr.	Congenital hemolytic jaundice Tower skull
Dt.R.	D	11	0	0	10.0	3.9	33	26	85	7.2	2.10		0.1	.42	.32	0	6		
Ar.R.	D	9	+	+	8.0	3.3	24	24	73	6.3	2.35	13	9	.58	.38	0	20	Incr.	Congenital hemolytic jaundice Tower skull
Al.R.	S	8	0	0	10.0	4.0	33	25	84	7.2	2.08		0.2	.40	.30	0	5		
W.R.	S	7	0	0	9.0	3.4	30	26	88	7.3	2.10		0.3	.40	.30	0	5		
Do.R.	D	5	+ (x-ray)	0	8.5	3.2	22	26	70	6.2	2.35	12	9	.60	.38	0	12	Sl.Incr.	Congenital hemolytic jaundice
H.R.	S	4	0	0	10.0	3.6	33	28	91	7.8	1.90		0.2	.38	.24	0	3		
Cn.W.	D	22m	0	0	9.0	4.3	31	21	72	7.1	1.85		0.8	.38	.26	0	5	Normal	
J.W.	D	7w	0	0	9.5	3.9	25	24	64	6.7	1.85		3.8	.44	.34	0	4		
Co.W.	H	40	0	0	14.0	5.0	40	28	80	8.1	1.54		0.3	.36	.22	0	4		

D - Daughter
S - Son
H - Husband

Significant data are underlined.

cause of nutritional deficiencies (see Table 1). In the youngest of the children (J.W.), anemia was distinctly microcytic, but there was no spherocytosis and fragility of red cells was within normal limits. One of the boys (Al.R.) had a suggestion of a "tower-shaped" skull without any Roentgen-ray evidence of increased marrow activity. The second husband (Co.W.) showed approximately normal hemoglobin and red cell count but his mean corpuscular diameter was low and red cell fragility was distinctly decreased. One of his children (Cn.W.), and the youngest child by the first husband (H.R.) also showed decreased fragility. In none of these 3 persons, and for that matter in none of the members of the entire family, was there any evidence of the sickling trait. All members belonged to blood group O, Rh positive, and all, with the exception of the mother, were serologically negative. All were dark brown in color and had distinct Negroid features.

Comment. The diagnosis of congenital jaundice in all 3 cases is well established by the typical clinical and laboratory findings and the familial incidence. Skull roentgenograms in Cases 1 and 2 are quite characteristic of a chronic hemolytic process, or better, of marrow hyperplasia associated with this condition. Such changes in the bones are more often seen in Cooley's anemia or sickle cell anemia, but are occasionally found also in congenital hemolytic jaundice.[1]

Hemolytic crises occurred in Cases 1 and 2 on one occasion simultaneously. These simultaneous crises in several members of a family have been commented upon by some observers.[3]

The rarity of congenital hemolytic jaundice in the Negro race raises the question as to whether the few reported cases are caused by admixture of white blood.[5] Such admixture was obvious in some cases,[7] but not in others. The family presented here as well as the one studied by Stragnell and Smith[6] were typical Negroes as far as facial features and color of the skin are concerned. If true cases of congenital hemolytic jaundice in African natives, similar to the one reported by Merskey and Baskind[4] are found, then the hypothesis of miscegenation will become unnecessary.

Summary. 1. Three typical cases of congenital hemolytic jaundice were encountered in a Negro family consisting of 10 persons.

2. In 2 of them, mother, aged 38, and daughter, aged 9, the disease was quite severe, accompanied by hemolytic crises and typical Roentgen-ray changes in the bones of the skull. In the third case, daughter, aged 5, there were typical blood changes, but as yet few clinical manifestations.

3. Review of the literature shows that congenital hemolytic jaundice is very rarely found in the Negro race.

We are indebted to the staff of the Paterson General Hospital for data of previous admission in Cases 1 and 2, and to the staff of the Valley View Country Sanatorium for some of the clinical and roentgenological data in Case 3.

Miss Selma Peller and Miss Gerda Petzall gave valuable technical assistance.

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BLOOD VOLUME STUDIES IN MIDDLE-AGED AND ELDERLY MALES

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RECENT reports of reduction in blood volume in patients suffering from chronic infections and malignancies[1,6] suggest the possibility of similar changes in individuals with chronic degenerative diseases. In reviewing the literature, however, no systematic studies of blood volume in normal elderly individuals could be found. The only study containing relevant data is that of Gibson and Evans,[3] who included measurements on 5 males above 50 years of age. Before conclusions concerning the effects of chronic degenerative diseases can be drawn it is necessary to know whether significant changes in blood volume occur with advancing age. The purpose of the present study was to gather data on plasma volume and total blood volume in elderly males exhibiting no clinical evidences of disease.

Materials and Methods. BLOOD VOLUME STUDIES: The blue dye T1824 (Wm. Warner & Co.) was used for measuring plasma volume, according to the method of Gregersen.[4] Optical density measurements were made on the Model 14 Coleman spectrophotometer at a wave length of 610 mμ. Serum was used for the colorimetric determinations instead of plasma in order to minimize hemolysis, since Gregersen and Schiro[5] found no significant changes in dye levels before and after coagulation of the blood. The total blood volume was calculated from the plasma volume and the venous hematocrit, utilizing a correction factor of 0.96 x hematocrit to compensate for plasma trapped among the cells.[5] Hematocrit determinations were done by the Wintrobe method in which the specimens were centrifuged at 3000 rpm for 30 minutes.

SELECTION OF SUBJECTS: Subjects were selected from the population of the Infirmary Division of the Baltimore City Hospitals using the following criteria: All subjects were ambulatory, had no recent surgical operations, and were free from any acute or chronic infections. Individuals were, however, included who exhibited occasional coarse rales with some morning cough over a period of years (by history and notation in the medical record) indicative of chronic bronchitis, a common finding in the Baltimore area. None of the subjects showed any evidence of fluid retention, ankle edema, constant fine moist rales at the lung bases, enlarged liver or abdominal fluid. All patients with a history of liver disease, heart failure, or exertional dyspnea were excluded. Hypertension *per se* was not disqualifying. Individuals with arteriosclerosis in various forms and to varying degrees were included. None of the subjects tested was receiving medication of any kind.

To assure constancy of conditions, all acceptable subjects were transferred from the Infirmary Division to the Gerontology Ward of the Hospital the day before the test. All blood volume studies were made in the morning under basal conditions; that is, no food or fluids were available after 8 p.m. on the evening before the test; tests were run at 8 a.m. the following morning while the patient was still in bed, before breakfast was served. The height and weight (nude) of each subject were recorded immediately following the test. Plasma and total blood volume per kg. body weight were calculated for each subject.

Results. No evidence of change in plasma or blood volume per unit of body weight was found in observations collected on 60 male subjects between the ages of 50 and 90 years (Table 1). Plasma volume ranged from a minimum of 31.29 cc. per kg. in a person 77

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years old (Subject 30) to a maximum of 62.47 cc. per kg. in a 53 year old person (Subject 4). The range in total blood volume was from 54.33 cc. per kg. in a 77 year old man (Subject 30) to 100.60 cc. per kg. in a man of 71 years (Subject 43). A comparison of the values obtained in the present study with the observations of Gibson and Evans[3] on young adults is shown in Fig. 1. Variations between subjects were large even within a single age decade.

No significant change with age was

TABLE 1.—PLASMA VOLUMES AND TOTAL BLOOD VOLUMES FOR 60 MALES ABOVE THE AGE OF 50 YEARS

Subject No.	Age Yrs.	Weight kg.	Height cms.	Plasma Volume cc./kg.	Total Blood Volume cc./kg.	Hematocrit %
1	50	59.54	157.48	57.40	98.48	43.4
2	57	61.36	170.82	49.29	84.42	43.3
3	55	56.59	157.48	44.95	77.77	44.0
4	53	65.91	164.47	62.47	96.23	36.6
5	56	47.50	157.48	54.86	92.53	42.4
6	50	78.41	173.99	49.18	82.29	44.1
7	57	62.27	168.91	37.72	70.90	48.8
8	67	74.09	169.55	45.11	78.18	44.1
9	68	54.32	157.48	55.14	87.37	38.4
10	68	47.72	--	42.33	82.35	50.6
11	68	57.86	165.10	58.57	96.65	41.0
12	64	63.41	161.29	38.72	68.77	45.5
13	63	87.95	173.99	41.38	67.29	40.1
14	65	47.60	153.67	51.58	83.19	39.6
15	63	75.46	175.26	53.81	86.39	40.0
16	64	65.46	179.07	47.68	76.17	39.0
17	61	66.14	166.37	40.12	68.36	43.0
18	68	66.36	163.83	56.10	81.31	32.2
19	61	56.82	167.64	44.22	76.12	43.6
20	64	65.00	168.28	40.52	70.97	44.7
21	61	63.64	161.29	39.97	67.52	42.5
22	69	68.64	158.75	43.27	74.85	44.0
23	67	71.82	168.28	32.48	60.83	48.5
24	65	82.27	177.80	51.79	84.49	40.3
25	64	70.91	169.55	56.64	99.18	44.7
26	73	59.54	157.48	40.14	72.72	46.7
27	71	50.91	161.93	48.22	94.93	51.2
28	78	62.27	165.10	53.89	85.00	38.1
29	70	51.59	163.56	44.79	77.35	43.9
30	77	82.27	167.64	31.29	54.33	44.2
31	70	74.09	171.45	41.85	71.66	43.3
32	72	56.14	163.83	54.00	92.00	43.0
33	71	52.27	160.02	51.79	87.18	42.3
34	75	49.77	161.29	52.09	89.83	43.7
35	78	45.68	165.74	44.22	76.12	43.6
36	70	63.63	160.66	44.87	71.68	39.0
37	70	56.36	163.20	44.06	75.09	43.1
38	70	54.54	142.24	54.91	97.89	45.7
39	76	60.45	157.48	42.22	74.32	45.0
40	74	63.18	165.10	45.35	79.83	45.0
41	71	77.50	160.02	50.58	79.78	38.1
42	70	50.45	153.04	48.80	81.32	41.7
43	71	60.00	165.10	59.78	100.60	42.3
44	79	64.32	167.64	43.89	71.95	40.6
45	83	73.86	163.83	38.13	—	—
46	81	64.09	160.02	50.10	82.09	39.50
47	82	55.45	166.37	46.25	76.72	41.40
48	82	65.23	166.37	38.45	60.39	42.9
49	88	50.00	154.94	60.86	93.48	36.4
50	87	61.36	154.31	49.12	82.28	42.0
51	83	66.36	165.74	50.91	81.86	39.4
52	88	61.14	160.66	47.25	76.46	39.8
53	82	68.40	168.28	40.71	61.66	35.4
54	81	55.23	166.37	55.46	87.88	38.4
55	85	57.05	166.37	46.52	84.28	46.7
56	85	64.77	173.99	53.05	84.47	38.7
57	86	57.50	172.72	56.21	98.43	44.7
58	87	45.00	157.48	54.82	94.35	43.6
59	87	55.23	157.48	49.12	79.74	40.0
60	90	40.91	163.56	60.30	98.53	40.4

found in mean plasma or blood volume in the present study (Table 2). Statistical analysis of the data from Gibson and Evans[3] also failed to demonstrate a significant change with age in younger subjects. However, the average values for plasma volumes obtained in the present study were slightly higher than those reported by Gibson and Evans (Present study, Mn=48.00 cc. per kg.; Gibson and Evans, Mn=43.19 cc. per kg.; difference=4.81 cc. per kg. t=3.57).

In order to minimize factors contributing to lowered or increased blood volume, subjects were carefully selected. In addition to the problems of fluid retention, which lead to increased blood volume, every attempt was made to exclude any factor which might produce a lowered blood volume. Taylor *et al.*[7] observed a diminution in the blood volumes of normal young males during periods of prolonged bed rest. To obviate the possibility of this factor confusing the study, only ambulatory

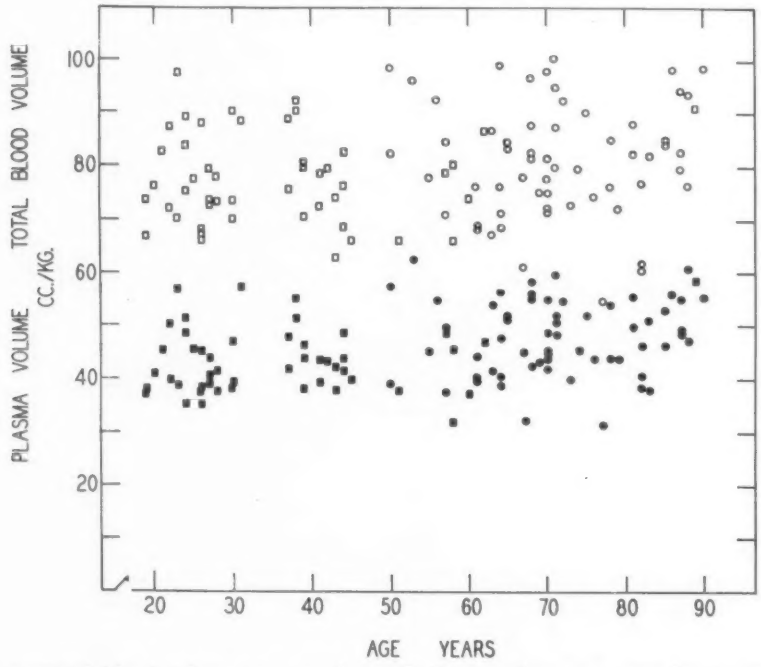

FIG. 1.—Total blood volumes, cc. per kg. and plasma volumes, cc. per kg. in 105 males. ☐ Total blood volume determinations from Gibson and Evans[3]; ■ Plasma volume (Gibson and Evans[3]); o Total blood volume, present study; ● Plasma volume, present study.

Discussion. Gibson and Evans,[3] observing 5 males above the age of 50 years, state: "Analysis of absolute and relative volumes by decades . . . shows a tendency in both sexes for values to remain at or rise above the average levels in the series during middle life and to decline with advancing age." This is not in keeping with the findings in the present study in which no changes with age were observed.

subjects were used. The Infirmary population has, within the 6 months prior to the study, been surveyed roentgenographically for tuberculosis, and all patients with suspected active tuberculosis have been removed for further investigation along these lines. None was included in this study. As stated above, all subjects were hospitalized the night before determinations were made in order to make the condi-

tions surrounding the test as homogeneous as possible.

Since no systematic age trend was observed in either study, the slightly higher values obtained in the present study, as compared with the results of Gibson and Evans,[3] may be attributed to differences in technique. The previous investigations used the multiple sampling procedure,[2] whereas in this study the single 10 minute sampling technique was used.

TABLE 2.—STATISTICAL ANALYSIS OF AGE CHANGES IN PLASMA VOLUME, TOTAL BLOOD VOLUME, AND HEMATOCRIT IN MALES

	Data from Gibson and Evans[3]			Data from present study			
	19-29 yrs.	30-39 yrs.	40-49 yrs.	50-59 yrs.	60-69 yrs.	70-79 yrs.	80 plus yrs.
	Plasma volume cc. per kg.						
Mn	42.33	45.54	42.34	50.84	46.64	47.19	49.83
N.	21	11	9	7	18	19	16
S.D. distr.	5.57	5.38	3.04	7.61	7.27	6.39	6.70
S.D. mn	1.24	1.70	1.07	3.11	1.76	1.49	1.73
	Total blood volume cc. per kg.						
Mn	77.34	81.95	73.50	86.09	78.33	80.71	82.84
N	21	11	9	7	18	19	15
S.D. distr.	8.09	8.06	6.20	9.36	10.06	10.97	10.99
S.D. mn	1.81	2.54	2.19	3.82	2.44	2.55	2.83

Summary. Blood volume determinations utilizing the dye T1824 and the 10 minute sampling method of Gregersen[4] were made on 60 normal males above the age of 50 years. The data obtained were analyzed statistically by decade subdivisions. Similar statistical analytic procedures were applied to data obtained from a study by Gibson and Evans[3] on individuals below the age of 50. No significant changes in blood or plasma volume per unit body weight were observed with increasing age.

Conclusion. From the data presented it is concluded that plasma volume and total blood volume per unit body weight in males do not significantly change with age.

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THE HEART IN FUNNEL-SHAPED AND FLAT CHESTS

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The term funnel-shaped is used to describe the type of chest usually observed in persons of slight build and characterized by depression of the lower end of the sternum and the costochondral ends of the 4th to the 9th ribs. This results in a distinct diminution in the antero-posterior diameter of the chest at the level of the xiphoid process. Other terms for this deformity are, trichterbrust, pectus excavatum and chone-chondrosternum. The flat chest is one with a small postero-anterior diameter of the entire thorax. Both types of deformity are not uncommon and are often associated.[24] Although the heart is often shifted to the left, in the majority of patients symptoms are either absent or insignificant. However, symptoms and signs may be present and may simulate and must be distinguished from, organic heart disease, rheumatic or congenital.[5,8,9,12,16,19a,b,25,31] In rare instances the sternal depression is extreme, producing erosion of the vertebral column and right heart failure.[14,30]

Material: This report comprises a series of 25 patients with funnel or flat chest referred for consultation because of a presumptive diagnosis of organic heart disease. The latter was excluded in each case by means of physical examination, electrocardiogram, Roentgen-ray and fluoroscopic examination.

Results. An analysis of the findings is presented in Table 1. Although the ages ranged from 5 to 56 years, all but 3 of the patients were under 40. The average age was 29.5 years.

Men predominated 4 to 1, the same ratio as that reported among cases in the literature. However, the ratio is disproportionately high in our series since the majority of cases were seen in military service; of the 10 cases seen in private practice 6 were men. One other writer, Kuhns,[16] also noted a 1 to 1 ratio.

Four-fifths of the patients were of asthenic habitus, several being extremely tall and thin. None of the patients was obese or of the pyknic type. The chest was funnel-shaped in 16 patients and flat in 2. In the remaining 7 there was a combination of flat and funnel-shaped chest.

The majority of the patients were of a nervous temperament. Ten patients complained of both precordial pain and dyspnea; palpitation occured in 6, dizziness and fatigue each in 4, joint pains and fainting twice. These symptoms have been observed by other writers.[1,4,5,9,10,21,24]

A loud systolic murmur was present in 60% of the cases and is a common finding.[8,9,17,24,28,30] In 2 cases the heart seemed enlarged in the postero-anterior view but this was disproven by study in the lateral and oblique positions (Fig. 1). The heart was definitely displaced to the left in 16 of the 25 patients. In 8 cases the left border of the heart was "straight" and in 10 the pulmonary artery segment appeared abnormally prominent (Fig. 2A.3), suggesting "mitralization."[25]

TABLE 1.—DATA ON 25 PATIENTS WITH FUNNEL OR FLAT CHEST

TABLE 1.—DATA ON 25 PATIENTS WITH FUNNEL OR FLAT CHEST

	Case	Age	Sex	Weight	Height (inches)	Referred Reason	Xray of Chest	PHYSICAL EXAMINATION				Electrocardiogram
								Systolic Murmur	Blood Pressure	Heart Rate	Neurocirculatory Asthenia	
1.	H.C.B		M			Enlarged heart.	Normal.	-			-	Right axis deviation, abnormal P-waves.
2.	T.B. *		M	145	69	Enlarged heart.	Pul art. prominent	-	120/80	64	+	Negative.
3.	C.S.D. *	32	M	190	73	Precordial pain.	Normal	-	118/60	76	+	Negative.
4.	L.C.D. *		M			Precordial pain, Dyspnea, Dizziness	No x-ray taken	-			+	No electrocardiogram taken.
5.	R.M.D.	22	M	155	63	None.	Apex displaced, pulm. art. prominent	-	110/60	72	+	Right axis deviation.
6.	W.E.	34	M	196	69½	Precordial pain, Enlarged heart, Joint pains.	Apex displaced, straight left border.	+	134/94		+	Negative.
7.	J.C.G. *	17	M	135	67	Fatigue.	Apex displaced.	+	116/74	85	+	Right axis deviation.
8.	J.G. *	21	M	130	70	Systol. murmur, Tachycardia.	Apex displaced, pul. art. prominent, straight left border.			88		Negative.
9.	D.D.L. *	42	M	145	69	Systol. murmur, Dyspnea, Dizziness, Fatigue.	Apex displaced.	+	110/70	74	+	Negative.
10.	J.L. *	18	M	160	69	Systol. murmur, Dyspnea, Joint pains.	Apex displaced, straight left border.	+	130/80	80	-	Abnormal P-waves.
11.	H.C.L. *		M			Systol. murmur.	Apex displaced	-	124/80	86	-	Right axis deviation.
12.	C.G.S. *	25	M	166	71	Systol. murmur.	Apex displaced.	-	110/70	72	-	Negative.
13.	J.S.S. *	38	M	155	75	Precord. pain, Dyspnea, Palpitation, Tachycardia.	Pul art. prominent, straight left border.	+	120/82		+	Right axis deviation.
14.	M.R.V. *	32	M	140	70	Palpitation, Premature beats	Apex displaced, pul. art. prominent.	-	130/80	85	-	Negative.
15.	D.R. *	24	F	122	66½	Systol. murmur.	Apex displaced, pul. art. prominent, straight left border.	-		80	-	Negative.
16	N.M.C. *	5	M	52	47½	Systol. murmur, Dyspnea, Enlarged heart.	Apex displaced.	+	94/54	76	-	Right axis deviation.
17.	M.F.	39	F	132	62	Systol. murmur, Precordial pain, Palpitation, Premature beats.	Normal.	+	140/80	70	-	Negative.
18.	R.S.	33	F	128	64½	Precord. pain, Dyspnea.	Apex displaced, straight left border.	+	112/74	68	+	Negative.
19.	F.S. *	28	F	87	61	Precord. pain, Dyspnea, Palpitation, Fatigue.	Normal.	+	142/80	66	+	Negative.
20.	A.S. *	39	M	120	64½	Systol. murmur, Dizziness.	Normal.	+	122/84	84	+	Negative.
21.	P.W. *	56	M	116	65½	Precord. pain, Dyspnea.	Apex displaced, pul. art. prominent.	-	130/70	72	-	Right axis deviation.
22.	P.H. *	21	M	118	67½	Precord. pain.	Pul. art. prominent.	+	146/80	70	+	Negative.
23.	H.U. *	41	M	172	73	Precord. pain, Palpitation.	Straight left border.	+	136/82	64	+	Abnormal P-waves.
24.	E.M. *	22	F	114	71½	Systol. murmur, Palpitation, Dyspnea, Dizziness, Fatigue, Tachycardia.	Apex displaced, pul. art. prominent.	+	135/80	90	+	Right axis deviation.
25.	W.F.T. *	21	M	130	67	Systol. murmur, Dyspnea, Tachycardia.	Apex displaced, pul. art. prominent straight left border.	+	116/76	95	+	Right axis deviation.

* Asthenic Habitus.

The electrocardiogram was usually normal, yet right axis deviation was present in 5 cases (Fig. 2B) and a tendency to it in 4. This incidence is greater than that found in normals for the age group of our patients. In normal persons without chest deformity in this age group there would probably be none with right axis deviation and a good many with left. In a number of electrocardiograms QRS was small in Lead 1 (Fig. 4). Left axis deviation was present only once. Cases 1 and 10 revealed large or notched P-waves in Leads 2 and 3 (Fig. 2B, 4). Thus, the electrocardiogram is that seen in persons of asthenic habitus and in neurocirculatory asthenia.[20] The electrocardiogram in funnel chest has been reported normal or showing some degree of right axis deviation[10,13,30] or even left axis deviation.[15] Grieshaber[13] in addition found changes in the T-wave in Leads 2 and 3. Teplick and Drake[31] reported minor changes in the chest leads. Premature beats, sinus arrhythmia and other irregularities occur occasionally.[10,15,23,24,30]

The following brief case histories are typical and illustrate the importance of the differential diagnosis of funnel chest from organic heart disease, particularly chronic rheumatic valvular disease.

Case Histories. CASE 1. J.C.G., a young man, aged 17, was referred because of easy fatiguability. Physical examination revealed a slender youth weighing 135 lbs. and 5 ft. 7 in. tall. There was a distinct depression of the lower portion of the sternum. A thrill was present and a short high-pitched systolic murmur was heard at the apex. A rough grating systolic sound was audible in the pulmonary area. The apex of the heart seemed to be shifted upward and to the left. This displacement was confirmed by roentgenographic examination (Fig. 2A). The electrocardiogram revealed right axis deviation; evidence of myocardial involvement was not present (Fig. 2B).

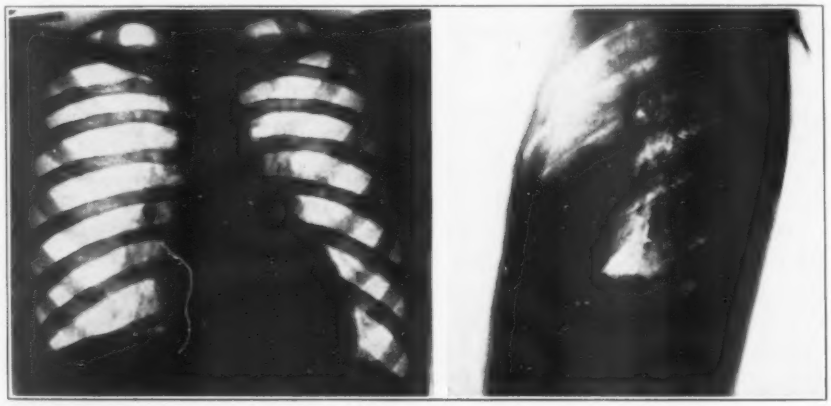

FIG. 1. (Case 22).—H. H., man, aged 21 years. The heart is round and full with a wide waist. It appears to be at the upper limit of normal in size, if not slightly enlarged. The lateral view shows the heart is in reality small and spread or "pancaked" out by the anterior chest wall and the depression of the lower portion of the sternum which almost touches the vertebral column.

The asthenia of this patient, the systolic murmur and thrill at the apex, the rough systolic murmur over the pulmonary area and the right axis deviation were attributed to the marked funnel-shaped depression of the sternum with displacement and rotation of the heart.

CASE 2. J.S.S., a man, aged 33, was referred because of sharp precordial pain, shortness of breath and episodes of rapid beating of the heart. Physical examination revealed a very tall, thin man 155 lbs. in weight and 6 ft. 3 in. in height. The chest was flat with a depression of the lower three-fourths of the sternum. A short systolic murmur was heard at the apex; the second pulmonic sound was accentuated. The blood pressure was 120/82 mm. Hg. Fluoroscopic and roentgenographic examination of the chest showed straightening of the left border of the heart and prominence

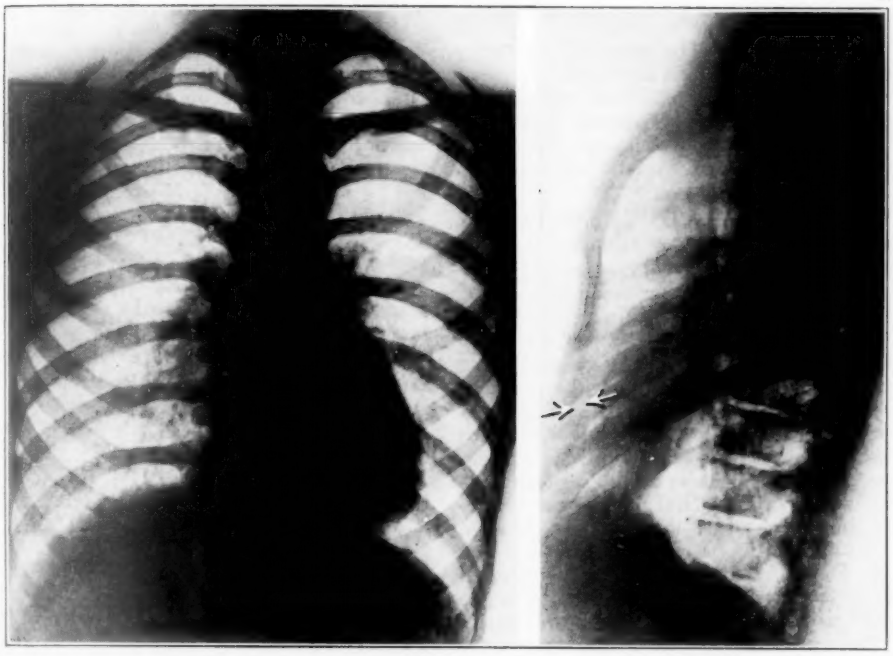

FIG. 2A

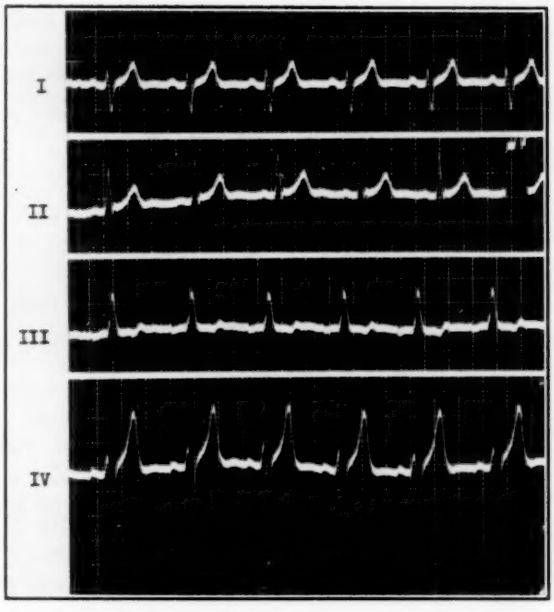

FIG. 2B

FIG. 2A. (Case 7).—J. C. G., boy aged 17 years. The teleroentgenogram in the postero-anterior position (left) shows the diaphragm low in the thorax and the heart and apex shifted to left. The left border of the heart is straightened and the region of the pulmonary artery is prominent. The right border is hidden by the vertebral column. The lateral view (right) shows the depression of the lower half of the sternum and the narrow antero-posterior diameter of the chest. The heart is small. FIG. 2B.—The electrocardiogram shows a normal sinus rhythm, rate about 90-95 beats a minute, with a right axis deviation of the QRS. The P (auricular) wave in Leads II and III are small, but wide and polyphasic.

of the right border. The resting electrocardiogram revealed right axis deviation.

The dyspnea, precordial pain and paroxysmal tachycardia were explained by the not uncommon association of these disturbances with flat and funnel-shaped chest and with neurocirculatory asthenia.

CASE 3. D.R., a woman, aged 24, had been refused admission to the Army Nurse Corps because of a systolic murmur over the pulmonic area. Physical examination revealed an asthenic woman, 122 lbs. in weight and 5 ft. 6½ in. in height. A funnel-shaped depression of the sternum was present. A harsh blowing systolic murmur was audible in the pulmonic area. Fluoroscopic and roentgenographic examination of the chest showed the heart shifted to the left and its left border straightened. The pulmonary artery segment was prominent. In the lateral position the anteroposterior diameter of the heart was seen to be small. The electrocardiogram showed left axis deviation. QRS-1 was slightly slurred and notched and T-3 was inverted but there was no evidence of myocardial involvement.

The systolic murmur was explained by the funnel-shaped depression of the sternum which caused the shift of the heart to the left, the straightening of its left border and the prominence of the pulmonary artery segment.

CASE 4. F.S., a woman aged 28, was referred because of dyspnea on exertion and following excitement, palpitation of the heart and nervousness. Physical examination revealed a thin woman weighing 87 lbs. and 5 ft. 1 in. in height. At the lower end of the sternum there was a funnel-shaped depression. At the mitral and apical regions a blowing systolic murmur was heard. The first heart sound was strong but the second pulmonic sound was not accentuated. The blood pressure was 130/74 mm. Hg. The teleroentgenogram and fluoroscopy disclosed a heart somewhat smaller than normal. The electrocardiogram showed a tendency to left axis deviation.

The symptoms and signs were due to neurocirculatory asthenia in a person with a small heart and funnel-shaped depression of the chest.

CASE 5. H.H., a man, aged 21, complained of pain in the chest and inability to perform moderate physical exertion. Physical examination revealed a thin, tall man of 118 lbs. weight and 5 ft. 8 in. in height. The chest was flat and the lower end of the sternum was depressed. A short systolic murmur was heard at the apex, and the second pulmonic sound was accentuated. The blood pressure was 146/80 mm. Hg. Roentgenographic examination of the chest in the postero-anterior view revealed an apparently full-sized, globular heart. On fluoroscopy the pulmonary artery was prominent in the right oblique position, the lateral views showed that the heart was small, being "pancaked" to the right and left by the pressure of the sternum (Fig. 1). The electrocardiogram was normal.

The occurrence of chest pain in a thin young adult with a systolic apical murmur, marked accentuation of the second pulmonic sound, a heart pancaked in the center and a prominent pulmonary artery segment can be explained by the presence of a flat chest with a funnel-shaped depression of the sternum.

Discussion. Funnel chest has been attributed to various etiological factors. Numerous authers[2,3,5,7,8,9,32] take it to be the result of intra-uterine arrest of development of the sternum. Others believe it is familial[23,24] or attribute it to a development defect with abnormal lengthening of the ribs,[11] to bad posture,[16,24] rickets,[5,10,16,24] poliomyelitis,[5,10] syphilis,[16] tuberculosis[5,10] or trauma.[8,24,32] Evans[9] quotes Laennec as attributing it to cobbling shoes. It has also been considered a constitutional defect in the asthenic habitus, as is seen in neurocirculatory asthenia.[20] Grodel[12] in 1911 pointed out the similarity of symptoms in persons with neurocirculatory asthenia and funnel chest. Humberd[14] found this defect in tall, thin, nervous persons. Kuhns[16] stated that funnel chest was never seen in asthenic persons although exceptions have been noted.[24] In our series of patients none gave a history of rickets, poliomyelitis or congenital anomaly. We are of the opinion that funnel chest is a constitutional, familial defect associated with asthenic habitus. As in neurocirculatory asthenia the symptoms in funnel chest are neurogenic or the result of inadequacy of the small heart in its response to emotional and physical stress.[6,20,33,34]

Humberd[14] believed the most significant disability of funnel chest to be the psychological factor. Sixteen of our patients were labeled neurocirculatory asthenia. Wolf[33] believes that the low

position of the diaphragm in funnel chest accounts for the dyspnea.

The symptoms in funnel chest and in neurocirculatory asthenia, *i.e.*, precordial pain, dyspnea, dizziness, palpitation and fatigue, are common in functional disturbances of the heart. They often can be differentiated from similar complaints in organic heart disease; for example, the pain is usually diffuse, long-lasting and not related to effort. In both funnel chest and neurocirculatory asthenia the presence of tachycardia and arrhythmias, apical systolic murmurs, straightening of the left border of the heart, prominence of the pulmonary artery and the finding of right axis deviation and P-wave and T-wave changes in the electrocardiogram add to the simulation of rheumatic valvular or congenital heart disease. The left auricle is normal in funnel chest, whereas it is usually enlarged in rheumatic heart disease. Under roentgenological examination in funnel chest the displacement of the heart to the left may create an illusion of enlargement by bringing the right border into line with the vertebral column[25] (Fig. 3). Accentuation of the shadows of the right lung root may suggest pulmonary congestion, pneumonitis or a tumor (Fig. 3). The cloudiness in the medial aspect of the lung is probably caused by the sternal depression[25] (Fig. 3) which also distorts the ribs so that they slant more sharply than usually[13] and the lower ribs are abnormally long.[35] The diaphragm is low (Figs. 2A, 3). The heart is flattened and appears less dense.[8,9,25] (Fig. 1). The aortic knob may be obliterated and in the oblique or lateral positions the retrocardiac spaces are obliterated[9] (Figs. 1, 2A, 3). Rarely the heart is displaced to the right[24] and in one case[32] the heart was in the right chest cavity. Awareness of all these effects of funnel chest and careful roentgenological examination make the differential diagnosis from organic disease obvious.

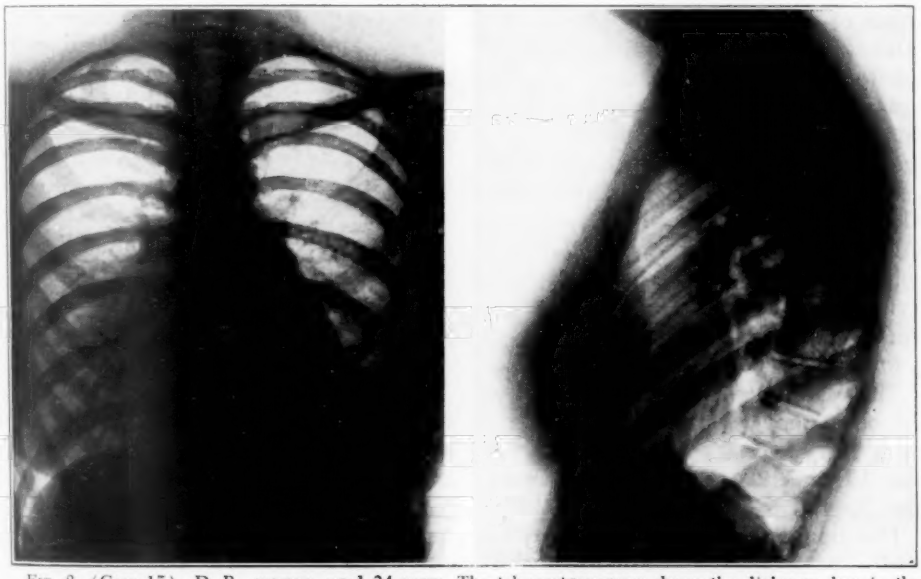

FIG. 3. (Case 15).—D. R., woman, aged 24 years. The teleroentgenogram shows the diphragm low in the thorax and the heart and apex shifted to the left. The left border of the heart is straight with fullness in the region of the pulmonary artery. The right border of the heart is lost in the vertebral column. The right hilar shadows are very prominent and the density of the lung appears to have increased at this point. In the lateral view the depression of the sternum is clearly seen, narrowing the antero-posterior diameter of the chest. The heart is small.

In rare instances the pressure of the sternum against the heart is so severe as to erode the thoracic vertebrae. Humberd[14] and Sweet[30] mentioned instances in which the sternum touched the vertebral column. There may be mechanical pressure on the right auricle and ventricle, the pulmonary artery, the aorta, and the inferior vena cava. Farmer[10] described right-sided enlargment. Levine[18] was of the opinion that heart failure is rare but that it may result from mechanical factors such as kinking or constriction of the large vessels leading to or from the heart, or from changes in the lung. The heart may be "pancaked" that is, flattened out, instead of displaced to one side or the other (Fig. 1). Brown[3] stated that the greatest cardiac embarrassment appears when the heart is fixed near the midline and is directly compressed by the depressed sternum. Pressure on the pericardium may produce milk spots. The vital capacity may be diminished. Kuhns[16] and Farmer[10] found the lung volume reduced. Others[16,24] have described interference with the mechanism of respiration when the diaphragm is low.

The patient with funnel-shaped or flat chest may, of course, develop organic heart disease like any other person. When this occurs the deformity may aggravate the cardiac disability.

The diagnosis of funnel chest may be made by inspection and roentgenographically. The patient is usually of slender build and the recession of the lower portion of the sternum is apparent (or in a flat chest the entire thorax is narrow). The apex of the heart may be displaced to the left and perhaps elevated. Evans[9] is of the opinion that a diagnosis of funnel chest should be made in adults only when the external postero-anterior diameter of the chest measures less than 6½ inches. He obtained this figure after studying normal chests in which he found the diameter never less than 7 inches and the average 7¾ inches. According to criteria of Kuhns[16] the ratio of the side to side diameter to the postero-anterior diameter should be more than 2.5 to 1; the ribs are relatively long and slender; the anterior arcs slant down sharply (the subcostal angle should be less than 90 degrees); the angle of Louis is less than 170 degrees, instead of being in a straight line, and the diaphragm is usually low. Paul and Richter[25] confirm the foregoing and suggest that in the postero-anterior Roentgen-ray view search should be made for the following: displacement of the heart to the left with a tendency to "mitralization," indistinctness of the right heart border which becomes lost in the shadow of the spine, decreased density of the heart shadow with corresponding increased visibility of the spine and cloudiness of the medial aspect of the right lung due to compression of the lung by the depressed sternum.

When a patient with funnel chest presents dyspnea, palpitation and precordial pain based on autonomic imbalance or neurocirculatory asthenia, encouragement may prove to be the only treatment needed. Teplick and Drake[31] pointed out that usually no treatment is necessary although rarely corrective exercises have been recommended.[17,22,29] The necessity of resorting to surgery is extremely rare.[12] Successful operations have been reported[21,23,27,35] and Ochsner and Debakey[24] and Phillips[26] advise operation in severe cases. Humberd[14] recommended the administration of vitamin E, the avoidance of fatigue, exercise and correct posture.

Summary. The incidence of flat and funnel-shaped chests is greater than is generally recognized. The two deformities often coexist.

Organic heart disease was not present in 25 consecutive patients with this deformity who were referred for consulta-

tion because of cardiovascular signs and symptoms. These included a systolic murmur at the mitral and apical regions, precordial pain, shortness of breath, palpitation, dizziness, fatigue, joint pains and fainting spells, in the order of their frequency. A moderately loud systolic murmur at the apex was heard in the majority of the patients.

Many persons, if not the majority, with funnel chest have no complaints; when symptoms and signs occur they are usually functional and are similar to those observed in neurocirculatory asthenia or autonomic imbalance.

Rheumatic mitral valvular heart disease was the most frequent erroneous diagnosis, since systolic murmurs, straightening of the left border of the heart or prominence of the right border and the pulmonary artery were present in most of the patients. Furthermore, right axis deviation and abnormal P-waves were not uncommon in the electrocardiogram. Occasionally T-II and T-III were inverted.

The signs in a person with a flat or funnel-shaped chest may also simulate congenital heart disease, pulmonary neoplasm, pulmonary congestion or pneumonitis.

The etiology of funnel chest has been attributed to various factors and diseases but it is probable that in the vast majority of cases it is a constitutional defect in persons of asthenic habitus.

Rarely in the funnel-shaped chest there is extreme depression of the lower end of the sternum. Failure of the right side of the heart may occur, usually from pressure on a large vessel entering or leaving the heart.

The diagnosis of a flat or a funnel-shaped chest may be made by inspection of the patient from the side. Roentgenograms and fluoroscopy of the chest afford confirmatory evidence. The ordinary postero-anterior six foot Roentgen-ray film may miss the deformity.

Reassurance is usually the only treatment necessary. Surgical intervention is not indicated except under most exceptional circumstances.

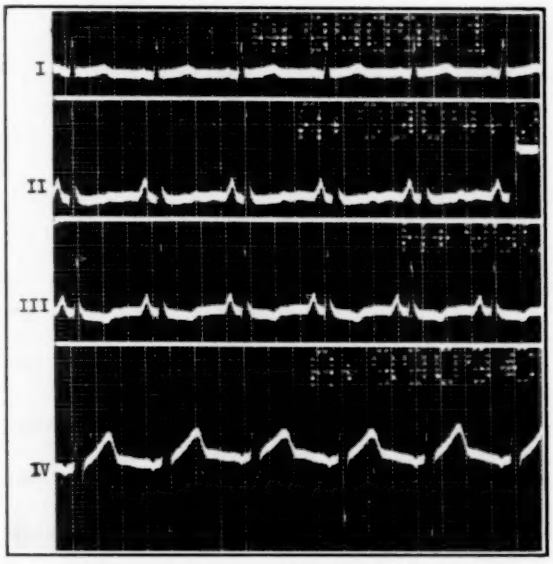

FIG. 4.—C. K. C., a tall, thin man of 43 years with a funnel-shaped depression of the lower sternum. A systolic murmur was present at the apex. The P (auricular) waves in Leads II and III are tall. The R wave in Lead I is small relative to the height of the R wave in Leads II and III. T_2 is semi-inverted and T_3 inverted.

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THE VALUE OF THE LABORATORY IN THE DIAGNOSIS OF POLIOMYELITIS

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With the approach of the poliomyelitis season each year the practicing physician looks to his colleagues in the field of epidemiology for new ideas to guide him in his clinical approach to this frightening disease. Each year knowledge accumulates, progress is made, and yet the goal remains elusive. Research in this disease has taken many courses and it would be idle to dwell further on these except to state that not infrequently the directions taken have proved tangential to the overall problem and have thus lost their ultimate value.

It is our opinion that today's ultimate in information regarding this disease can be obtained only in those centers where there exists teamwork between the practicing physician, the fever hospital, the virology laboratory, the public health investigator, and the research facilities of the medical school. Only under such ideal circumstances can an outbreak of poliomyelitis be studied to yield the greatest amount of factual data.

Unfortunately, one or several of these components is too often missing, and the report of an outbreak tells only a fraction of the story. Correlation of clinical material with laboratory data has often meant requesting aid from distant and frequently overburdened viral laboratories. This has proved difficult regardless of the highly cooperative spirit existing in these centers.

The urgent need for laboratory collaboration was vividly brought home to us during an outbreak of anterior poliomyelitis occurring in the late summer and fall of 1947 in the Milwaukee area. Eighty-seven patients required hospitalization at the South View Hospital in Milwaukee during this period.

Although the signs and symptoms showed some deviation from those seen in previous epidemics, the predominant factor was the absence of paralysis in all cases. The seasonal incidence of this outbreak concurred with that of previous epidemics. There were no deaths attributable to the disease, and autopsies of patients who expired in the hospital during this period revealed no pathologic changes characteristic of poliomyelitis.

In this epidemic skeletal muscle involvement was limited to varying degrees of spasm. The severe cases were relieved simply by the application of hot compresses during the usual 14 days of hospitalization; ten cases required further similar treatments at home for periods of one to three weeks. This is in direct contrast to our experience of former years where severely afflicted patients were transferred to other institutions for continuation of their long periods of convalescence and physical therapy.

Epidemics of poliomyelitis appear to vary as to the clinical manifestations which predominate during each out-

break. This is illustrated by a comparison of the following charts which include the epidemic years of 1937, 1946, and 1947.

The year 1937 was selected for comparison because it presented a rather typical picture of a moderate poliomyelitis outbreak with mean percentages of deaths, residual paralysis, and nonparalytic cases. The year 1946 was felt to be important for comparison because of the wide variation of case types from that of the subsequent year, 1947.

TABLE 1.—PREDOMINANT SYMPTOMS

	Percent		
	1937	1946	1947
Fever	69.6	92.1	90.8
Nausea and vomiting	42.1	32.5	75.8
Headache	62.7	30.2	87.3
Neck and back rigidity	63.7	70.2	86.2
Irritability	61.8	29.3	35.6
Lethargy	44.1	6.5	44.8
TOTAL CASES	102	215	87

Table 1 indicates the predominance of fever, nausea and vomiting, headache, and rigidity of the back and neck in the 1947 series of cases. Severe headache was such a prominent feature of the 1947 outbreak alone that we feel it requires special emphasis. Lethargy was as prominent in 1947 as in 1937, but was almost absent in 1946.

The admission spinal fluid cell counts as compared in Table 2 signify a somewhat greater cellular response in the 1947 series.

The distribution according to sex, as shown in Table 3, reveals no significant variation.

The distribution by age groups indicates that approximately three-fourths of the patients in each series were in the age group below 16 years. In 1947 there was a slight increase in the number of adults over 31 years of age who were afflicted.

Table 5 confirms the absence of skeletal muscle involvement in 1947 as previously stated. The spasm was almost fleeting in some instances, lasting only a few hours, while in others it was more persistent. There were 3 patients with soft palate weakness of a transitory nature.

Personal communications from pediatricians in the Milwaukee area during the 1947 epidemic revealed that many patients presented symptoms of nausea, vomiting, mild headache, low-grade fever, and malaise. The duration of symptoms was relatively short, 12 to 24 hours, and the picture simulated that of mild cases admitted to the hospital. This suggests that the epidemic included many other cases not admitted to the hospital. Although an investigation was undertaken to determine the rather unusual nature of this outbreak, unfortunately facilities for the isolation of virus strains were not available.

Agglutination studies on 8 sera samples obtained 6 weeks after the onset of symptoms were reported negative for choriomeningitis, St. Louis encephalitis, and equine encephalomyelitis. We are indebted to Dr. Charles

TABLE 2.—INITIAL SPINAL FLUID CELL COUNT PER CC.

	Percent		
	1937	1946	1947
Under 10 cells	5.9	8.4	4.6
10 – 49	32.4	32.2	34.5
50 – 99	26.5	25.2	13.8
100 – 199	22.6	21.6	22.9
200 – 299	11.7	7.6	11.5
300 – 399		1.8	2.3
400 – 499			4.6
500 – 599	0.9		1.2
Over 600		0.4	2.3
Bloody specimens		2.8	2.3

Armstrong of the National Institute of Health, Division of Infectious Diseases at Bethesda, for his kind cooperation and laboratory aid. Tests for antibodies against poliomyelitis were omitted, and single convalescent samples give insignificant results.

Discussion. Our data reveal that 87 cases of suspected anterior poliomyelitis were admitted in 1947 to the South View Isolation Hospital of the Milwaukee Health Department. The symptoms presented fulfilled the criteria neces-

sary for a diagnosis of poliomyelitis. The histories, physical examinations, sedimentation rates, and spinal fluid findings were consistent with the diagnosis.

In October certain evidence came to light which gave rise to the question of the presence of an entirely different entity. The chief factor, inconsistent with the diagnoses, was the absence of residual paralysis and black muscle spasm. In no case was it necessary to apply hot compresses after the third week following discharge from the hospital. No cases required further hospitalization or physical therapy following discharge from the isolation hospital, with the exception of an 18 month old non-resident baby with deltoid paralysis. This case was omitted from the data due to its origin outside the Milwaukee area.

TABLE 3.–DISTRIBUTION ACCORDING TO SEX

	Percent		
	1937	1946	1947
Male	54	111	48
Female	48	104	39
TOTAL CASES	102	215	87

Although the spinal fluid reaction was consistent with the diagnosis, the clinical picture challenged it. We, therefore, reviewed the 1937 and 1946 series. A comparison of the 3 series revealed a higher incidence of nuchal rigidity and headache in the 1947 series, giving rise to the possibility of encephalitis or encephalomyelitis instead of poliomyelitis.

It is quite evident from the data at hand that we are assuming the presence of poliomyelitis in our community. It is also evident that certain additional factors must be considered: (1) The presence of an attenuated or unusual virus strain; (2) The existence of partial immunity; and (3) The possibility of an entirely unrelated encephalomyelitis.

Not until adequate laboratory facilities are made available will further epidemiological studies of this nature be conclusive. It is our opinion that progress toward the eradication of at least the killing and crippling aspect of this disease will stem to a large extent from more comprehensive studies of the nature of the organism itself and the immunological reactions it produces. A network of viral laboratories with well-trained personnel serving at least the more densely populated communities must be developed if rapid progress is to be achieved. The absence of such a laboratory in a community frequently places the practicing physician in the unhappy position of entire dependence upon clinical signs and symptoms so often resulting in the diagnosis of "One of those virus affairs."

TABLE 4.–DISTRIBUTION BY AGE GROUPS

	Percent		
	1937	1946	1947
0 – 5 years	35.3	31.2	26.4
6 – 10	26.5	26.1	27.6
11 – 15	17.7	21.9	20.7
16 – 20	7.8	8.8	5.8
21 – 30	3.9	7.8	8.0
31 and over	8.8	4.2	11.5

Our experience in the 1947 outbreak of a disease we have chosen to call non-paralytic poliomyelitis served as an example to us of how important was the need for virology laboratories. Techniques for the identification of many viruses have in recent years become applicable to the less elaborate laboratories. This advance has placed the viral laboratory in the category of a working counterpart, rather than an expensive and impractical luxury for every sizable fever hospital throughout the country.

TABLE 5.–DISTRIBUTION OF PARALYTIC AND NON-PARALYTIC

	Percent		
	1937	1946	1947
Paralytic Cases	78	121	0
Non-paralytic Cases	24	94	87
TOTAL CASES	102	215	87

It is our hope to establish such a viral laboratory at the South View Isolation

Hospital within the near future. We thus hope to obviate the impracticability of burdening distant laboratories with material which at present must be minimal and delicately handled and often unsuitable for research value.

With such an addition to this institution we feel we will be in a position to serve better the almost one million population of the Milwaukee Area and to contribute materially to the advancement of knowledge concerning poliomyelitis and other viral diseases.

Summary. 1. An outbreak of a disease resembling poliomyelitis occurred in the Milwaukee area during the summer of 1947.

2. This disease varied in certain unusual respects from the "typical" poliomyelitis outbreaks seen in previous years and was strikingly different from the outbreak seen the year before.

3. Sera from afflicted patients of the 1947 outbreak did not reveal the presence of several types of encephalitis in this group. However, no studies could be made of the stools of these patients for the presence of the poliomyelitis virus.

4. The need for facilities to study patients for the presence of poliomyelitis and other viruses exists in most fever hospitals throughout the country. Southview Isolation Hospital in Milwaukee is no exception to this need.

5. The authors believe that when the viral laboratory becomes an active part of most fever hospitals, definite progress will be made in the study of the nature of poliomyelitis and the answers to its protean nature.

ELECTRO-NARCOSIS: RESULTS IN 125 PATIENTS WITH PSYCHOSIS OR PSYCHONEUROSIS

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Electro-narcosis is the word used to designate a state of unconsciousness or semiconsciousness produced by passing an electric current through the brain. The term was introduced by the French worker Leduc in 1902[2] in describing early experiments with such technique. Van Haareveld with various co-workers reported experiments in animals with electrically induced alteration of consciousness in 1934 and again in 1942 and 1943.[4] The first experiments in man were reported by Frostig, van Haareveld, Resnick, Tyler and Wiersma in 1942.[1] The real impetus to this work was given by the report of Tietz and her co-workers in 1945. Since then other reports have been made by Tietz on a larger group of patients and by workers from England on initial studies.[3a,b]

This report deals with the first two years' experience of the author and those working under his direction in giving electro-narcosis to 125 patients (Table 1). With few exceptions, the patients had all been subjected to other forms of treatment which had produced little or no improvement and were in the poor prognostic situation of having been ill for long periods. The diagnostic groups treated were chiefly schizophrenia, paranoid and catatonic types; manic depressive psychoses; involution psychoses; psychoneuroses with chronic compulsive anxiety; and a few in scattered other groups chiefly for experimental reasons.

Technique. The technique of Tietz is followed in detail. Patients are treated in the fasting condition; a small amount of fluid before the treatment is considered permissible, however. Bladder and bowel should be empty. The patient lies on a bed or table. A pillow is put lengthwise under the back from lumbar to cervical regions. Placement of the electrodes is critical. We use the external auditory meatus and the zygomatic arch as reference points and place the electrodes with the posterior edge of the electrode 2 inches (5 cm.) anterior to the external auditory meatus, and the inferior edge of the electrode 1½ inches (3 cm.) above the zygoma. If the patient shows during the treatment any respiratory difficulty, the electrodes are advanced to a position 2½ or 3 inches forward from the meatus in subsequent treatments; if there is too much restlessness, a more posterior position is used. The position of the electrodes is marked with a pencil and ruler before application of the electrode paste, after which the electrodes are put in position and held down by a rubber band similar to that used in electroshock treatment. It is usually advisable to use an absorbing insulator of gauze or paper towel under the band over the forehead to avoid current being shunted across the electrodes by a layer of perspiration. The usual safeguards for the tongue, gauze or rubber, are then placed in position, and in addition a

TABLE 1.–NUMBER OF TREATMENTS OF ELECTRO-NARCOSIS GIVEN TO 125 PATIENTS

	Number of Patients	Total Treatments	Average Number of Treatments per Patient
Group A–State Hospital Patients	43	1038	24
Group B–Author's Private Patients and those treated for other physicians	82	1533	19
TOTALS	125	2571	

rubber airway of suitable size is partially inserted between the gauze or rubber props (we never use the word "gag"). The airway should be of suitable size to avoid injury to pharyngeal structures which may cause hemoptysis. At this point, 0.25 to 0.40 gm. of pentothal sodium is injected intravenously rapidly. Within 5 to 15 seconds the patient falls deeply asleep and within a few more seconds becomes apneic. The apnea lasts from 15 to 40 seconds. Then after 3 or 4 breaths, preferably of 5% CO_2 in O_2, the current is applied through the electrodes.

On a suitable chart are recorded at 15 second intervals the milliamperes of current used in each treatment. There are also recorded the muscle tension, state of respirations and any other pertinent data. The initial current level of 150 to 350 m.a. is not applied in full force instantaneously with the throwing of the switch. It is gradually raised from zero to the peak level over a period of 2.5 to 5 seconds, preferably with an automatic electronic control, but a skillfully handled manual control will do as well. To this slow initial current rise, Tietz has applied the term "glissando" borrowed from the musical lexicon. With the slow initial rise of current the body musculature is not jolted to sudden maximal tonicity, but is brought gradually to maximum tone with less danger to skeletal integrity. After a few seconds, if the current level is adequate, a general extensor movement of the musculature is seen. This is the signal that a major epileptiform seizure has been produced. If it fails to occur by 10 to 12 seconds, the experienced operator raises the current level manually to produce the desired effect. Then after 5 to 10 seconds the current level can be dropped more or less gradually to reach a level of 50 to 60 m.a. between 25 and 40 seconds from the onset. During this process the end of the epileptiform seizure should be evident in the occurrence of softened clonic movements. At the end of this seizure the patient may breathe immediately or after varying periods of apnea. At this point, the assistant inserts the airway completely and starts continuous suction of oral and pharyngeal secretions through suitably placed rubber catheters and administration of 5% carbon dioxide and oxygen through a mask.

Apnea should cause no concern until 60 seconds have passed, since the carbon dioxide and oxygen can be administered through the airway under positive manual pressure from the rebreathing bag. Cause of persistent apnea should be evident to the experienced operator. It is usually persistent tonicity of the respiratory muscles and can be quickly relieved by dropping the current to 25 or 30 m.a. for a few seconds, and then returning it to 50 m.a. when respirations start. Excessive difficulty of this variety is the chief reason for more anterior placement of the electrodes. The skillful worker can often move the electrodes quickly during the treatment but this is not a procedure for the beginner. If the patient does not respond quickly to current manipulation, the treatment should be stopped and tried another day with proper change in electrode placement.

Between 45 and 75 seconds, as a rule, respirations are well established. The patient at this point is usually flaccid. The current should then be gradually raised, 5 or 10 m.a. every 15 seconds, to the point at which strong ("4 plus") flexor rigidity of the arms is obtained, usually between 2.5 and 4 minutes. In some patients marked extensor tone precedes the flexor rigidity for varying periods. The end point of useful tone is indicated by laryngeal inspiratory stridor. This cannot be allowed to become severe and interfere with respiratory exchange. The occurrence of inspiratory stridor is often preceded by a period with expiratory grunt which is harmless. During the presence of maximum tone and regular respiration the patient is relatively quiet and may be considered to be in an adequately narcotized state. At this level, fine clonic movements or tremors of the legs and more rarely arms may be observed. The tonicity noted in the arms does not always involve the legs, which may be almost flaccid.

If the initial seizure is inadequate, or if the current is not properly raised to an adequate level, or if the electrodes are placed too far anterior, the patient may show semi-voluntary movements of resistance and inadequate unconsciousness (as usually indicated by his subsequent complaint). Such restlessness during the treatment is considered undesirable and the patient cannot be said to have an adequate electro-narcosis.

The proper current level is maintained until 7 minutes from the beginning of the treatment in most patients. The current may then be abruptly turned off as was described in the original technique. The author believes, however, that gradual dropping of the current to zero over a period of 2 to 4 minutes is desirable because this produces in most patients a state of flaccid relaxation which is the complete antithesis of the pathologic tension for which they are being treated and which is, therefore, considered beneficial. The tonic level can be safely maintained in most patients for much longer than 7 minutes but only in a few patients refractory to treatment, has this been found useful or necessary.

After the current is turned off the patient usually appears to be in a natural sleep. Remaining excessive secretions in the mouth and throat are aspirated and several extra

breaths of carbon dioxide and oxygen are allowed. Patients remain asleep for varying periods, from 10 minutes to 2 hours. After 10 minutes practically all can be aroused and all are oriented for time, place and person, and have only minimal, if any, memory defect until many treatments (at least 15 or 20) have been given. Most private patients can be returned to open medical floors or home to their families within one hour. State Hospital patients can be returned to "home" wards or to various occupations with which they may be entrusted usually in less than one hour.

PHYSIOLOGIC CHANGES. Numerous and various physiologic changes take place during this treatment. The chief neurologic changes have been described. Electro-encephalographic changes are less marked than with classic electroshock. Psychologic studies show less "organic" impairment of function after treatment than after classic electroshock. The cardiovascular system is strongly affected. During the initial high current level, the heart is usually irregular, but regularity returns promptly when the current level is reduced. During the treatment, the blood pressure rises (both systolic and diastolic) 50% to 100% above the original levels. This is not dangerous unless there is advanced arterio-sclerosis. One of our patients was a hypertensive individual who safely received 18 treatments. In one of these, his pressure readings were 230+/130 at 45 seconds of electro-narcosis, 280+/120 at 3 minutes, 270/170 at 5½ minutes, 270/? at 7½ minutes and 230/120 at 8 minutes, which was 15 seconds after the current was turned off. Rise in blood sugar and leukocytes is further evidence of adrenergic activation. Marked perspiration and salivation are practically invariably present. We have not seen, during the treatment, involuntary urination or defecation, or seminal emissions. Nausea may follow the treatment if the patient has improperly eaten a large meal; but this is unlikely if no more than a small amount of liquid food is ingested. We have observed no fractures in our cases and to date there have been no deaths directly attributable to the treatment. One patient died by accident or purposely in a tub of scalding water, not on a treatment day.

TABLE 2.—RESULTS OF ELECTRO-NARCOSIS TREATMENTS

	Private Patients*				State Hospital Patients§			
	A	B	C	D	A	B	C	D
Involution psychoses								
Melancholia	1					1		
Paranoid type	1					1		
Psychoneuroses	3	2						
Manic depressive	4	6	4		1	2	1	1
Schizophrenia								
Hebephrenic			3	1		1	4	3
Catatonic	2					1	1	1
Paranoid	1	8	2		2	6	5	1
Other groups		1	1				1	1
TOTALS	12	17	10	1	3	12	12	7

* 6 patients incomplete (private) § 9 patients incomplete (State hosp.)
A: Complete remission; B: "Social" recovery; C: Improved; D: Unimproved.

THE NUMBER OF TREATMENTS varies from patient to patient. In our group, we have regarded 15 treatments as a minimum, and many have received over 30. A few have had 50 or more. Treatments are administered three times weekly for the first 3 or 4 weeks, then twice weekly until a good remission is obtained. During the latter part of this period, the treatment is usually given as an "ambulatory" procedure. It may be given on an ambulatory basis from the beginning to properly chosen patients. After the re-

mission is obtained, experience indicates that relapses will be minimal if "maintenance" treatments are continued once weekly over a long period, several months in some patients. This seems to allow the patients to resume normal environmental relationships and responsibilities safely, while consequent tensions are continuously dissipated through the treatment as long as they continue to develop. Their development gradually subsides under such technique in our experience.

Indications for the treatment are most clearly derived from the results obtained in various groups of patients. Only the patients under the author's control are considered in the tabulated results (Table 2).

Results. The results of treatment here reported are to be interpreted with the important consideration that almost all of these patients had been subjected to other forms of treatment, chiefly insulin and electroshock, alone or in combination. The patients, therefore, represent a group of treatment failures by previous standards. Among the private patients 29 of 41 are thought by strict criteria to be much improved or recovered, 10 improved to a less degree, and only 1, a schizophrenic of 20 years illness, unimproved. Of the 10 "improved", 6 are still hospitalized, 1 is employed, and 2 are active housewives and 1 is a retired clergyman, much better adjusted. With further attention the results in these should improve further. Follow-up periods are not sufficiently long to make the results conclusive but the rate of relapse within 6 months of completing treatment is not more than 2 in 15, and these are patients out of our control. The other patients are continuing to improve in their social and industrial adaptation in a manner which previous experience with other treatments indicates will continue to be productive and useful. The State Hospital patients present a different, but essentially no less favorable aspect. They are all suffering from chronic illness, resistant to previous intense treatment. In some who are only moderately improved, the electro-narcosis has been the means of achieving for the first time a peaceful hospital situation. The potential benefit from treatment in these patients is often obstructed by difficult family situations and the adverse State Hospital surroundings. In spite of this, several outstanding cases present themselves as useful social individuals after long and apparently hopeless mental invalidism. Our continuing work with these people is developing, as far as conditions permit, in greater individualization of management and more prolonged treatment.

The most favorable diagnostic groups, according to the official classification, for application of electro-narcosis are the affective psychoses: the depressed manic depressive and melancholic involution psychoses; the paranoid psychoses in both schizophrenic and involution groups, including late developing paranoid conditions difficult to classify and sometimes called "paraphrenia"; and the catatonic reactions, both depressed and excited. In addition, a limited number of individuals with psychoneurotic reactions, chiefly evident in "compulsive" anxiety characterized by repetitious self-disparagement and self-accusation, religious scruples, and the like, have been treated. Apparently, if any one characteristic can be seen which runs through the entire group, it is the presence of deep anxiety, otherwise unapproachable by any means whatever. It is such anxiety which the electro-narcosis alleviates, in the author's opinion, as no other method, with the possible exception of lobotomy, can.

Brief case reports of a few neurotic individuals with "compulsive" anxiety and guilt relieved by this treatment will be of interest:

Case Reports: CASE 1. Rev. T., a clergyman who over a period of years became unable to carry on his work, celebrate mass, hear confessions, etc., experienced a total failure with Insulin. After electro-narcosis, he has resumed all of his duties, no longer feels contaminated or unworthy.

CASE 2. H. R., a man of 30, with chronic syphilophobia, was previously partly relieved by intensive psychotherapy and electroshock, but had a recurrence in much more severe form after 2 years with associated somatic symptoms, headache, dizziness, dyspepsia. He was relieved by electro-narcosis and returned to work and normal marital relationship.

CASE 3. T. J., a girl of 19, was totally disabled by a sense of guilt associated with religious scruples and obscene thoughts of characteristic "ruminative" variety. She failed to improve with electroshock, but was much improved by electro-narcosis, so that she could help with work at home, and go to church; only 8 treatments were given, which we considered inadequate, but we could not secure further cooperation from the family.

CASE 4. H. C., a man of 50 who had developed a ruminative anxiety about having sold a prosperous business, suffered from total sleeplessness and marked agitation. After treatment, he became a cheerful, energetic man; moved to California and bought a new business.

CASE 5. V. V., a woman of 28, was beset by religious scruples and feelings of sinfulness, unworthiness and contamination. After 20 treatments she was able to work as a cashier in a college cafeteria, have dates, enjoy social contacts and is able to see with some humor her remaining symptoms.

In our experience dangers of the treatment are minimal or non-existent. As previously stated, there have been no skeletal complications. One patient suffered the loosening of a tooth. No cardio-vascular complications have occurred, even in the one patient with severe hypertension, and several with inactive rheumatic heart disease. We consider active organic disease of the brain (such as recent hemiplegias and untreated neurosyphilis), acute infections, recent cardiac lesions or failure, and severe renal deficiency as contra-indications to this treatment. In 2 patients we have seen the delirium, called by some authors the "amnestic reaction", after a number of treatments. As in the same type of reaction occurring after ordinary electroshock treatment, the condition clears in a period of 7 to 21 days, without residual difficulty.

Summary. (1) The technique of electro-narcosis is described in detail.

(2) Very favorable results in private patients and moderately favorable results in State Hospital patients have been obtained after previous treatment failures by other measures.

(3) The treatment, in common with the more classical electroshock, is without appreciable danger.

(4) Anxiety, whether expressed as a psychotic reaction with depressive, paranoid or catatonic features, or as a neurosis, is the chief indication for the treatment.

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STUDIES UPON THE RELATION BETWEEN PLASMA ANTITHROMBIN AND HEPARIN*

I. INFLUENCE OF PLASMA ANTITHROMBIN ON PROTHROMBIN TIME

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Kazal and Arnow[9] found that lyophilization of normal human plasma did not cause an appreciable loss of prothrombin, provided that marked alteration of the normal plasma pH was avoided. The "loss" reported by other investigators[15] appears to be an artefact produced by restoration of the plasma by distilled water or with improper solutions of carbonic acid. Kazal and Arnow found that the optimum pH for determination of plasma prothrombin values of lyophilized citrated human plasma, using Quick's method, was between 7.4 and 7.8, and that in this range the prothrombin values very closely approximated those of the original plasmas. Tocantins[17] found that a loss of prothrombin activity occurred when citrated or oxalated plasmas were exposed to an *air current*. A simultaneous increase in pH occurred. The prothrombin activity could be brought back to essentially normal by the treatment of the aereated plasma with CO_2. Quick[11] repeated Tocantin's experiments and reported aereation of dog and rabbit plasma at 38°C. did not cause a loss of prothrombin activity.

Banfi, Tanturi and Bay[2] observed that a loss of prothrombin activity occurred gradually in *stored* human plasma after 4 or 5 days. This "loss" was to a certain extent only apparent and due to the formation of an antithrombin in *stored* plasma. The influence of this antithrombin on the prothrombin time of stored plasma was easily shown when *stored prothrombin-free plasma* was used as a diluent.

In the course of experiments undertaken to prepare a stock of lyophilized prothrombin-free plasma for use as a plasma diluent, we found an increase in the natural antithrombin activity when compared to the same plasma before lyophilization. This was demonstrated by determining the "thrombin time" of both samples.

The following experiments were undertaken in an attempt to study: a) the antithrombin activity of various plasmas, and b) the influence of this antithrombin activity on the determination of prothrombin time by using a one-stage method. Experiments were carried out on fresh normal plasma, aged normal and prothrombin-free plasmas, aereated normal and prothrombin-free plasmas and lyophilized normal and prothrombin-free plasmas of dogs.

Material and Methods. *Blood.* The blood used throughout these experiments was obtained from fasting unanesthetized mongrel dogs through femoral artery puncture. The blood was drawn into dry syringes, immediately transferred into 15 cc. graduated centrifuge tubes containing sodium oxalate solution in the proportion of 9:1, and then centrifuged for 10 minutes

*Aided by a grant from the Lois C. Grunow Surgical Fund.

after which the plasma was pipetted into dry test tubes.

Prothrombin determinations were done by the one stage method of Quick[12] as modified by Tanturi and Banfi,[16] using a lyophilized thromboplastin prepared from acetone dried triturated rabbit brain. Thromboplastin so prepared was extremely stable.[9]

Prothrombin-free plasma was prepared by treating normal oxalated plasma with a 30% suspension of barium sulfate.[16] Washing of the suspension was carried out, using distilled water made neutral by the synthetic resin polyethylene polyamine methylene. This procedure made the suspension more stable. Repeated testing of the plasma so prepared failed to show any evidence of clotting or fibrin precipitates when mixed with the calcium-thromboplastin mixture and observed for as long as 18 hours at 37°C. The specific adsorbant character of barium sulfate for prothrombin has been confirmed by others.[4,14]

Thrombin and *"thrombin times":* Two different thrombins, both of which gave equivalent results, were used. One was prepared from human plasma using the procedure of Eagle;[5] the other was the so-called "hemostatic globulin" (Lederle). Both the human thrombin in dilution 1:10 and the "hemostatic globulin" in dilution 1:20 gave similar "normal" thrombin times of 17 to 20 seconds when 0.1 cc. of thrombin solution was mixed with 0.2 cc. of oxalated dog plasma. In every experiment the dilution of hemostatic globulin with distilled water was freshly prepared and its strength tested against a control of a fresh sample of plasma.

Procedures Employed in Treatment of Plasmas. *Lyophilization* was accomplished after preliminary freezing in a mixture of methyl cellusol and crushed solid CO_2. Reconstitution was achieved by the addition of neutral distilled water to the original volume. The lyophilized plasmas were kept either in vacuo or stored in a dessicator over calcium chloride at room temperature (20°–25°C.).

TABLE 1. THROMBIN TIMES OF DIFFERENT PLASMAS ASSAYED

Plasmas	Number of Experiments	Time in Seconds Range	Average
Fresh	60	17–20	18.5
Fresh prothrombin-free	68	17–20	18.5
Stored (16 days)	18	20–30	25
Stored prothrombin-free (16 days)	10	20–30	25
Stored (29 days)	8	40–60	50
Aereated	5	50–60	55
Aereated prothrombin-free	4	50–60	55
Lyophilized	40	50–100	75
Lyophilized prothrombin-free	45	50–100	75

To 0.2 cc. of plasma were added 0.1 cc. of hemostatic globulin (Lederle) diluted in distilled water in proportion 1:20. All determinations were carried out in duplicate in test tubes 12 by 75 mm. at 37° C.

Stored plasmas: These were kept covered in a refrigerator (5°C.).

Aereated plasmas: Procedures similar to those described by Tocantins[17] and Quick[11] were employed. In all these experiments care was taken to prevent bubbling and consequent surface denaturation. When CO_2 was blown over alkaline plasmas care was taken not to shift the pH beyond 7.

Solutions and Reagents. *Water:* In the early part of the study ordinary distilled water was used but later distilled water treated with the synthetic resin polyethylene polyamine methylene was used. The water so treated is neutral.

Protamine solutions were prepared by dissolving 100 mg. of protamine

sulfate (Lilly) in 100 cc. of distilled water. Such solutions showed a tendency to deteriorate and were frequently prepared. The pH of the fresh solution was 7.0. When deterioration occurred, the solution had a pH of 6.3 and had lost most of its activity.

Sodium oxalate solutions were prepared by dissolving 1.34 gr. sodium oxalate per 100 cc. distilled water.

Calcium chloride solutions were 0.025 molar (0.28 gr. per 100 cc.) and *normal saline* solutions, 0.9%. All reactions were carried out in duplicate in test tubes 12 by 75 mm. at 37°C.; all measurements of volume with volumetric flasks, volumetric or serological pipettes (0.2 cc. graduated to 0.001 cc.); and time measurements with a stop watch graduated to 0.2 seconds. pH determinations were done using a glass electrode potentiometer.

Results: In Table 1 the "thrombin times" of the various plasmas are compared with those of fresh plasmas. In Table 2 the effect on the prothrombin times of a *normal sample* of plasma by diluting it with the variously treated plasmas can be seen. It is apparent that the lengthening of the prothrombin times parallels the anti-thrombin activity of the different plasmas used as diluents.

In Table 3 the influence of pH on the antithrombin activity of *aereated* or *lyophilized* plasmas when treated with CO_2 is shown. The different antithrombin activity found by us could be explained on the basis of differences of pH and accordingly the experiments recorded in Table 4 were done. In Table 5 the effect of CO_2 on the thrombin time and prothrombin time of *lyophilized plasmas* is recorded. It is shown that the loss of prothrombin activity of *lyophilized* plasma is only apparent and that the "loss" can be restored bringing the pH back to normal by treatment with CO_2. An excessive amount of CO_2 will produce an acid plasma with a lengthened prothrombin time consequent to a decreased prothrombin level.

TABLE 2. PROTHROMBIN TIMES OF FRESH PLASMA USING VARIOUS PLASMAS AS DILUENTS

Plasma Tested	Plasma Diluent	Prothrombin time (Dilution) 0	1/10	1/20	1/50
Fresh normal	Fresh prothrombin-free	12	17.6	23.3	33.6
Fresh normal	Aereated prothrombin-free	—	19	25	38
Fresh normal	Stored prothrombin-free	—	19.5	26	41
Fresh normal	Lyophilized prothrombin-free	—	24	32	60

Prothrombin times are averaged results of 14 determinations for each plasma diluent assayed.

TABLE 3. EFFECT OF CO_2 ON pH AND THROMBIN TIME

Plasmas	Before CO_2 Thrombin Time (*Seconds*)	pH	After CO_2 Thrombin Time (*Seconds*)	pH
Fresh	18	7.8	12	6.9
Fresh prothrombin-free	20	—	—	—
Aereated	30	8.1	16	7.0
Stored Prothrombin-free	43	8.2	18	7.4
Lyophilized	no clot in 2 min.	9.05	16	7.03
Lyophilized Prothrombin-free	no clot in 2 min.	9.0	15	7.0

To 0.2 cc. of plasma were added 0.1 cc. of hemostatic globulin (Lederle) diluted in distilled water in proportion of 1:20. All determinations were carried out in duplicate in test tubes 12 by 75 mm. at 37°C. Thrombin times are averaged results of 6 determinations for each plasma assayed. Ph determinations were done using a glass electrode potentiometer (Beckman). The source of CO_2 was crushed, dried ice. The current of CO_2 was passed through the plasma during a period of 5 to 10 seconds.

The variations of antithrombin activity and its direct influence on the prothrombin time of the plasma, although closely correlated with changes in pH, could also be interpreted as variations of activity of the "heparin complement" of these plasmas as affected by changes in pH. With this idea in mind, we studied the effect of protamine sulfate on the antithrombin activity of the different plasmas. In Table 6 the results of these experiments are recorded and it is apparent that protamine decreases the antithrombin activity of the plasmas studied.

TABLE 4. INFLUENCE OF pH ON THROMBIN TIME AND PROTHROMBIN TIME OF FRESH PLASMA USING DIFFERENT PLASMAS AS DILUENTS

THROMBIN TIME

Plasmas	Time (Seconds)	pH
Fresh	19	7.8
Fresh prothrombin-free	22	8.0
Stored prothrombin-free	43	8.2
Lyophilized prothrombin-free	no clot in 2 min.	9.09

PROTHROMBIN (Seconds)

Plasma Tested	Plasma Diluent	Dilution 0	1/10	1/20	1/50
Fresh normal	Fresh prothrombin-free	12	16	22	33
Fresh normal	Stored prothrombin-free	—	19.5	26	41
Fresh normal	Lyophilized prothrombin-free	—	19.7	31.1	50.5

To determine the effect on the prothrombin time of the reduction of the antithrombin activity by protamine, the following experiments were done, first using fresh prothrombin-free plasma and lyophilized prothrombin-free plasma as diluents of normal fresh plasma and then comparing the results of the prothrombin times so obtained with the prothrombin times of samples of the same fresh plasma similarly diluted with protamine treated lyophilized prothrombin-free plasma (Table 7). Many similar experiments were done, but these results were not constantly obtained, not because the plasmas varied regarding the interaction of protamine and antithrombin, but because an excess of protamine exerts a depressant effect on prothrombin as can be seen by the experiments recorded in Table 8. On the other hand, not only the different plasmas studied, but also the normal or fresh plasmas, varied widely in their antithrombin activity. Thus, the accurate adjustment of the quantity of protamine to be added to decrease the antithrombin activity without further decreasing prothrombin activity, or concentration, was difficult (Tables 6, 8, 12).

The influence of protamine was checked in regard to its effect on the pH of plasmas. In Table 9 this lack of change of pH is clearly shown and the decrease of antithrombin activity is notable. The reduced antithrombin activity is also reflected on the prothrombin times. In Table 10 similar experiments, which were carried out in an attempt to demonstrate the lasting effect of protamine on the pH and antithrombin of lyophilized plasma, are recorded.

We have also studied the effect of protamine on the antithrombin activity and pH of lyophilized human plasma and the results are recorded in Table 11.

In view of these results, the effect of the addition of increasing the amount of protamine on the antithrombin activity and prothrombin time of stored and fresh normal oxalated plasma was

studied, using samples of blood obtained from 3 dogs (Table 12). It is shown that fresh plasmas varied in their "normal" antithrombin activity, so undoubtedly the quantities of protamine added influenced the prothrombin activity and the fibrinogen. This is in contrast with the wider range observed when protamine is added to lyophilized or stored plasmas with high antithrombin activity.

Comments: The increase of antithrombin activity of plasma after 4 to 5 days' storage as found by Banfi, Tanturi and Bay has been confirmed. The increase of antithrombin activity is not related to the presence of prothrombinemia to the alkalinity of lyophilized plasma due to the lack of CO_2. We have confirmed the results of Kazal and Arnow in regard to the effect of CO_2 in bringing the prothrombin time of lyophilized plasma of dogs back to normal,* but we regard the changes observed in prothrombin times as being more closely related to the enhanced antithrombin activity brought about by the process of lyophilization. This antithrombin activity is reflected on the prothrombin times of the lyophilized plasmas as well as on the normal fresh plasmas when prothrombin determinations of the latter are carried out using lyophilized pro-

TABLE 5. EFFECT OF CO_2 ON THROMBIN TIME AND PROTHROMBIN TIME OF LYOPHILIZED PLASMA

THROMBIN TIME

Plasma	Before CO_2 Time (Sec.)	pH	After CO_2 Time (Sec.)	pH
Lyophilized	no clot in 2 min.	9.05	16	—
Lyophilized prothrombin-free	no clot in 2 min.	8.9	18	7.03

PROTHROMBIN TIME (SECONDS)

Plasma Tested	Plasma Diluent	0	1/10	1/20	1/50
Lyophilized	Lyophilized prothrombin-free treated with CO_2	19	17	23	36
Lyophilized treated with CO_2	ID	13	15	20	30
Lyophilized After Repeated Treatment With CO_2*	ID	18	23	31	46

* This plasma after repeated treatment with CO_2 (pH 6.3) decreased its prothrombin. As it is known excess of CO_2 decreases prothrombin.

bin in stored plasma because similar increases of antithrombin activity occur in stored prothrombin-free plasma, lyophilized normal and prothrombin-free plasma and aereated normal and prothrombin-free plasma. That stored, aereated and lyophilized plasmas have prolonged prothrombin times has also been confirmed.

The decrease of prothrombin found by some investigators in aereated, stored and lyophilized plasmas is to some extent only apparent. In the case of *lyophilized* plasma, Kazal and Arnow attributed the apparent hypoprothrombin-free plasma as diluent. The fact that the lyophilized prothrombin-free plasmas also show an increase of the antithrombin activity points out that, to a considerable extent, the decrease of prothrombin observed by other investigators in similar conditions is due to an increased antithrombin activity in the clotting system studied.

The increased antithrombin activity of *aereated* and *stored* plasmas is also reflected in the prothrombin times of these plasmas and on normal plasmas in which the determinations of pro-

thrombin were carried out using aereated or stored prothrombin-free plasmas as diluents.

The increased antithrombin activity observed apparently exerts its effect on the second stage of coagulation which, in the one-stage methods of prothrombin determinations, appears to be an important factor in the resulting prothrombin time. It is generally agreed that the one-stage methods of prothrombin determination measure a clotting time which is theoretically the summation of the time corresponding to the conversion of prothrombin to thrombin (1st stage), and that of the conversion of fibrinogen to fibrin by the action of the thrombin already formed (2nd stage). It is easy to understand then that not only a decrease in the rate of conversion of prothrombin, concentration or any other interference in the first stage of the clotting mechanism will give a prolonged prothrombin time but any interference in the second stage will produce similar results. A good example of the second possibility is that of the presence of heparin in excessive amounts, such as is observed in the plasmas of anaphylactic or peptone-shocked animals, or in the plasmas of patients who have received intravenous injections of heparin to prevent thrombosis. In both cases, a definite prolongation of prothrombin time which is not due to a corresponding decrease of prothrombin concentration is observed.[3] When the one-stage methods of prothrombin determination are used to test *normal* plasmas, the influence of the antithrombin activity is overcome by the excess of thrombin which results from the addition of an excess of thromboplastin.

The results of our experiments on different plasmas with enhanced antithrombin activity emphasize the importance of the very frequently neglected factor of the variation of the anti-thrombin activity, and the equally neglected factor of the pH of the reagents in the clotting system under study.

TABLE 6. EFFECT OF PROTAMINE SULFATE ON ANTITHROMBIN OF DIFFERENT PLASMAS

Plasmas	Thrombin Time (Seconds) Before Protamine	After Protamine
1. Fresh normal	18	13.5
2. Fresh prothrombin-free	17	15.8
3. Stored (5 days)	30	20
4. Stored prothrombin-free (5 days)	30	14
5. Aereated	60	18
6. Lyophilized prothrombin-free	173	50

All samples received 0.3 mg. of protamine sulfate per cc. of plasma. Samples 5 and 6 received 0.65 mg. and 1 mg. of protamine sulfate per cc. of plasma respectively.

By treatment with CO_2 the antithrombin activity of the plasmas studied by us was brought back to "normal." Hence, the prothrombin times also became "normal," possibly through restoration of the pH optimal for coagulation. The demonstration that protamine sulfate does not change the pH, but does change the antithrombin effect, which is also reflected by the shortened prothrombin times, adds support to the belief that these changes are not solely due to changes in pH.

From the results of some of the experiments reported here, it can be said that protamine exerts a depressant effect on prothrombin. Some combination of protamine with prothrombin which would interfere with the conversion of prothrombin to thrombin might be the explanation. It has been shown[12] that when protamine and hep-

arin are present in proportions other than 3:1, which is the proportion found between heparin and protamine dosage in *in vitro* studies, then the substance in excess lengthens the clotting time. That this lengthening is not due to any interference in the 2nd stage of clotting is shown by the shortening of thrombin times obtained when protaing the 5 minute period of treatment prior to centrifugation. In any event, the clots we obtained were firm and similar to normal clots. Furthermore, any lack or decrease of fibrinogen would be reflected by a lengthening of the thrombin times.

As we have shown, protamine not only decreases the enhanced antithrom

TABLE 7. PROTHROMBIN TIME OF FRESH PLASMA USING LYOPHILIZED PROTHROMBIN-FREE PLASMA TREATED WITH PROTAMINE

Plasmas	Thrombin Time (Seconds)
Fresh	20
Fresh prothrombin-free	20
Lyophilized prothrombin-free	116
Lyophilized prothrombin-free + protamine	36

PROTHROMBIN TIME (SECONDS)

Plasma Tested	Plasma Diluent	Dilution 0	1/10	1/20	1/50
Fresh normal	Fresh prothrombin-free	12	18	22	30
Fresh normal	Lyophilized prothrombin-free	—	21	29	34
Fresh normal	Lyophilized prothrombin-free treated with protamine*	—	18	23	31.4

* To 3.5 cc. of chilled (8° C.) plasma 1.2 mg. of protamine sulfate was added. After 5 minutes at 8° C., the plasma was centrifuged.

TABLE 8. EFFECT OF PROTAMINE SULFATE ON THROMBIN TIME AND PROTHROMBIN TIME OF FRESH PLASMA

Plasmas	Thrombin Time (Seconds)
Fresh normal	20
Fresh prothrombin-free	19
Fresh normal + protamine (0.3 mg. 1 cc.)	15
Fresh prothrombin-free + protamine (0.3 mg. 1 cc.)	16

PROTHROMBIN TIME (SECONDS)

Plasma Tested	Plasma Diluent	Dilution 0	1/10	1/20	1/50
Fresh normal	Fresh prothrombin-free	13	18	23	33
Fresh normal + protamine	Fresh prothrombin-free + protamine	18	31	35	48*

* pH of lyophilized prothrombin-free + protamine at the end of experiment 8.7.

mine is added to normal plasmas. Mylon, Winternitz and Süto-Nagy[10] found that the addition of protamine to plasma leads to a rapid and extensive precipitation of fibrinogen. The temperature after addition of protamine influenced this precipitation. We believe that we have avoided extensive precipitation of fibrinogen by chilling the plasmas and by keeping their temperature between 5° and 8°C., durbin activity of lyophilized or stored plasmas, but also decreases the activity of the antithrombin of fresh plasmas. The similarity of action of protamine on heparin, protamine action on "normal" antithrombin activity and on the enhanced antithrombin activity of the plasmas studied lead to the belief that the differences in antithrombin activity observed in the plasmas studied is due to different quantities

of heparin present in them. We have found an approximate proportion between protamine and the antithrombin activity of normal plasma. A dose of 0.3 mg. to 0.4 mg. of protamine per cc. of plasma of dogs reduced the thrombin times of normal plasmas to an extent which cannot be further reduced no matter how much protamine is added. One mg. to 1.50 mg. of protamine per cc. of plasma produced a precipitation of fibrinogen which interferes notably with the reaction. As has been said above, a slight excess of protamine also influences the prothrombin activity in clotting systems in which this substance has been studied. The proportion between protamine and antithrombin activity of normal plasma is in contrast with the proportion between protamine and antithrombin activity of lyophilized or stored plasma. In the latter cases a greater quantity of protamine is necessary to bring the antithrombin activity back to normal.

The so-called normal antithrombin of plasma has been identified by Quick[13] as present in the albumin fraction but not in crystalline serum albumin as shown by Jaques and Mustard[8] and by Ziff and Chargaff[18]. As is well known, heparin acts only in the presence of this plasma fraction. According to Ziff and Chargaff the rate of clotting in a system containing thrombin, fibrinogen and heparin may depend entirely on the concentration of the heparin complement or normal antithrombin of that system. The same authors point out that the concentration of this complement in the blood may be the determining factor

TABLE 9. EFFECT OF PROTAMINE SULFATE ON THE ANTITHROMBIN AND pH OF PLASMA

Plasmas	Thrombin Time (Seconds	pH
Fresh normal	20.2	7.8
Fresh prothrombin-free	20.5	7.9
Lyophilized prothrombin-free	116	8.9
Lyophilized prothrombin-free + protamine	30	8.7

PROTHROMBIN TIME (SECONDS)

Plasma Tested	Plasma Diluent	Dilution 0	1/10	1/20	1/50
Fresh normal	Fresh prothrombin-free	12.9	16	22	31
Fresh normal	Lyophilized prothrombin-free		21	29.5	45
Fresh normal	Lyophilized prothrombin-free treated with protamine*		17.7	22.2	31.4

* pH of lyophilized prothrombin-free + protamine at the end of experiment, 8.7.

TABLE 10. DEMONSTRATION OF THE LASTING EFFECT OF PROTAMINE SULFATE ON pH AND ANTITHROMBIN OF LYOPHILIZED PLASMA

Plasmas	Thrombin Time (Seconds)	pH
Lyophilized prothrombin-free	no clot in 3 minutes	9
Lyophilized prothrombin-free + protamine	30	8.9
Lyophilized prothrombin-free + protamine and centrifuged	32	
After 35 mins. standing at room temp.	35	
After 65 mins. standing at room temp.	40	8.8
Uncentrifuged	30	
After 35 minutes standing at room temp.	36	
After 65 minutes standing at room temp.	42	8.8
Protamine sulfate	—	7.0
Thrombin solution	—	6.3

to the individual response to heparin. Astrup and Darling[1] found that the so-called normal antithrombin is not identical to the antithrombin substance formed from heparin. This last compound, called by them "thrombin inhibitor," inactivates thrombin more rapidly than the normal antithrombin.

The loss of CO_2 which is a common factor in the plasmas studied seems to be closely related to the behavior of the antithrombin activity. The close relationship between pH and antithrombin activity of plasmas points out that the antithrombin varies in activity according to the pH of the plasma. Fisher[6] found that while heparin combines with a large number of proteins under suitable conditions, the resulting heparin protein compound is inactive provided that it is stable at the pH of the assay. Jaques and Mustard[8] have obtained results similar to those of Fisher and state that if the reaction of heparin with the normal antithrombin of plasmas is similar to that of heparin with other proteins, it is probable that the isoelectric point of the normal antithrombin is more alkaline than the pH of plasma.

Our experiments show that the normal antithrombin activity of plasma increases with its alkalinity. However, the mechanism by which protamine inhibits the normal antithrombin activity of plasma is not easily understood.

Considering the basic character of protamine one possibility worthy of consideration is that the antithrombin

TABLE 11. EFFECT OF PROTAMINE ON ANTITHROMBIN AND pH OF LYOPHILIZED CITRATED NORMAL HUMAN PLASMA

Lyophilized plasma*	Thrombin Time (Seconds)	pH
Sample I	25	7.4
2 cc. of Sample I + 0.6 mg. protamine sulfate	14.6	7.4
Sample I (28 days old)	35	
2 cc. of Sample I (28 days old) + 0.6 mg. protamine sul.	25	
To the same sample was again added 0.6 mg. of pro. sul.	18	7.4

* Standard Navy and Army package (Parke Davis and Co.). After made up, the solution was kept in the refrigerator (5° C.).

EFFECT OF CO_2 AND PROTAMINE ON ANTITHROMBIN, PROTHROMBIN TIME, AND pH OF LYOPHILIZED CITRATED NORMAL HUMAN PLASMA

	BEFORE CO_2				AFTER CO_2			
Plasma Date	Thrombin Time (Sec.)	Prothrombin Time (Sec.)	pH	Volume (ML)	Time of CO_2 Passing Through (Sec.)	Thrombin Time (Sec.)	Prothrombin Time (Sec.)	pH
Sample II (4-VI)	70	66	9.27	2	3	27	45	7.6
				2	5	27	43	7.3
				2	10	24	49	6.9
				2	15	28	52	6.9
				2	25	20	85	6.5

Plasma*	Thrombin Time	pH
Sample I (1-V1) 2cc. of Sample I + 3 mg. protamine	55	8.9
	20	8.8
Sample II (4-VI)	70	9.2
2 cc. of Sample II + 3 mg. Pro.	28	9.2

* Standard Navy and Army package (Sharp & Dohne). This plasma was made up by adding 250 cc. of distilled water and kept in a refrigerator. Note the different quantities of protamine necessary to bring thrombin time back to "normal." Thrombin time and ph of a sample control normal fresh human oxalated plasma = 25 seconds and 7.5 respectively.

Considering the basic character of protamine one possibility worthy of consideration is that the antithrombin

activity of normal plasma is due to the presence of heparin bound to the cofactor. The compound displays a relatively slight activity on the normal pH of plasma. Protamine neutralizes heparin, and hence reduces the antithrombin activity without changing the pH of plasma. Opposite changes which shift the pH of plasma to the alkaline side will establish appropriate conditions which enhance the activity of the compound heparin-cofactor and so increase the antithrombin activity of plasma. The protein, or factor to which heparin is bound, would not necessarily have any antithrombin activity per se. Further studies are required to clarify the hypothesis advanced.

TABLE 12. EFFECT OF PROTAMINE SULFATE ON THE "NORMAL" ANTITHROMBIN ACTIVITY PROTHROMBIN TIME OF STORED AND FRESH PLASMAS OF SEVERAL DOGS

Dog No.	Tube No.	Volume (cc.)	Appearance	Protamine (Mg.)	Thrombin Time (Sec.)	Prothrombin Time (Sec.)
1	1	2	clear	—	16.8	12.6
	2	2	clear	0.05	15.	15.1
	3	2	clear	0.1	16	16
	4	1.45	clear	.15	14.5	17.4
	5	1.41	clear	0.20	15.8	16
	6	1.0	clear	0.25	12.6	20
	7	1.02	clear	0.30	12.9	19
2	1	2.0	clear	—	25	13
	2	2.0	clear	0.4	15.5	17.5
	3	2.0	clear	0.5	16.	18
	4	1.44	cloudy	0.9	13.8	21
	5	1.45	cloudy	1.0	11.6	20
		Tubes 4 and 5 centrifuged and the determinations repeated				
	4		clear		15	16
	5		clear		13	15
3	1	2	clear	—	16	13
	2	2	clear	0.4	14	17.5
	3	2	clear	0.5	13	20
	4	1.44	clear	0.2	13	19
	5	1.45	clear	0.4	12	20.5
stored plasma	1	2	clear	—	21.5	15.4
	2	2	clear	0.4	16.4	21
	3	2	clear	0.5	15.8	22
	4	1.44	clear	0.2	16	20.6
	5	1.45	clear	0.4	14	22.4

Conclusion and Summary. 1. Lyophilized, aereated and aged plasmas show an increase of antithrombin activity as compared with the corresponding fresh plasma. The antithrombin activity was studied using a thrombin solution of constant activity.

2. The increased antithrombin activity is not related to the presence of prothrombin because the same changes occur in lyophilized, aged and aereated prothrombin free plasmas.

3. The effect of the increased antithrombin activity is reflected in the prothrombin times of these plasmas and on the prothrombin times of fresh plasmas when plasmas with increased antithrombin activity are used as diluents.

4. The increased antithrombin activity may be brought back to normal by means of various treatments (CO_2, protamine).

5. The antithrombin activity varies directly as the pH of plasma. How-

ever, protamine sulfate decreases the antithrombin activity without changing the pH of the plasma. It may be concluded that the decrease of prothrombin noted by other investigators in similar plasmas is due to the presence of the antithrombin and not solely due to changes of the pH.

6. Protamine sulfate has a tendency to decrease prothrombin and precipitate fibrinogen depending upon the quantity present.

7. With appropriate quantities of protamine sulfate the antithrombin activity of fresh oxalated normal plasma can be reduced to a certain extent but no more, irrespective of the amount of protamine used. An approximate proportion between the quantity of protamine necessary to return to normal the thrombin times of certain plasmas and to reduce the antithrombin activity of normal plasmas has been demonstrated.

8. A hypothesis which suggests that heparin is the normal anticoagulant of plasma is presented.

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EFFECT OF STREPTOMYCIN ON BLOOD CLOTTING TIME AND PROTHROMBIN TIME IN MAN*

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Recently, Macht[6] reported that streptomycin when administered parenterally shortened the coagulation time in rabbits and cats. Farrington and his co-workers,[3] investigating streptomycin toxicity in man, performed occasional determinations of the blood clotting and prothrombin times, but found them to be normal. Since streptomycin is one of the important antibiotics in clinical use at present, it would seem desirable to determine the influence it may have on the clotting mechanism in man.

TABLE 1.–PERTINENT CLINICAL DATA IN STREPTOMYCIN AND CONTROL GROUPS OF PHTHISIC PATIENTS

	Streptomycin Group (No. of Cases)	Control Group (No. of Cases)
Total No. of Patients	21	21
Age (range in years)	19-57	21-57
Activity of Lesion*:		
Class 1	14	15
Class 2	7	6
Collapse Treatment:		
Thoracoplasty	4	4
Pneumothorax	3	1
Pneumoperitoneum	1	0
Lobectomy	1	0

* Clinical classification adapted from criteria of National Tuberculosis Association.[1]

Material. The patients selected for this study were 35 cases of pulmonary tuberculosis, 24 having far-advanced, 8 moderately advanced, and 3 minimal lesions. Of the 35 cases, 14 were receiving streptomycin in accordance with the protocol of the streptomycin research program of the Veterans' Administration, at the time this investigation was initiated. The remaining 21 were suitable controls. Seven of these were subsequently treated with streptomycin and retested as part of the streptomycin group. Thus the treated and control categories each comprised 21 cases, 7 patients being common to both. The pertinent clinical data for both groups are listed in Table 1. They were matched as carefully as was clinically feasible in all essential respects. Particular pains were taken to assure close comparability in respect to clinical activity, for it has been claimed[2,11,12] that the level of prothrombin in phthisis is related principally to the severity of the disease. To facilitate this, the patients were classified into two broad categories, adapted from the criteria of the National Tuberculosis Association[1]: Class 1: Activity none or slight; Class 2: Activity moderate or severe.

Methods. Two methods of investigation were employed: (a) Performance of repeated tests (3 to 5) at about the same time (from 1 to 2 hours following the morning dose of streptomycin) on different days over a period of several weeks. (b) Performance of tests serially, prior to and at 15, 30 and 90 minutes following the injection of streptomycin (or a control injection of distilled water).

Each patient in the streptomycin group received 0.5 gm. of streptomycin in 2 cc. of distilled water at 8:00 a. m. and 8:00 p. m. daily for 120 days by the intramuscular route. The average dose of streptomycin was 7.56 mg. per kg. per injection. The control patients were given 2 cc. of distilled water intramuscularly only during the performance of the serial tests.

All patients, otherwise, received substantially the same routine treatment of bed rest and symptomatic remedies as required.

Streptomycin blood levels were determined every 2 weeks by microbiological assay.[9] Blood for these estimations was usually obtained from 1½ to 2 hours after the morning dose. The average blood level for the group was 10 micrograms per cc. with a range of 5 to 40 micrograms. Streptomycin estimations could not be performed concomitantly with the serial tests, so that the actual levels at the time serial samples were taken is unknown.

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The presence of severe liver damage which might interfere with the response to streptomycin was sought for in all patients. None had clinical evidence of liver damage. Three streptomycin patients and 2 controls were found to have 3 plus cephalin flocculation reactions. However, a positive cephalin flocculation test alone was not regarded as significant of liver dysfunction unless confirmed by abnormal bromsulfalein retention; that is, more than 10% in 45 minutes, using 5 mg. per kg.

Blood was withdrawn with stasis from an antecubital vein by means of a 20 gauge needle into a syringe previously coated with mineral oil. Frothing was prevented by avoiding suction. If the vein was not entered on the first attempt, the needle was changed and another vein selected for puncture. The portion of blood withdrawn last was used for the Lee-White test. The rest of the blood was mixed with 1/10 volume of 0.1 M sodium oxalate in a conical tube, centrifuged at 2,000 r.p.m. for 10 minutes, and the supernatant plasma used for determination of the prothrombin time.

Blood Coagulation Time: The following modification of the Lee-White method was used: 1 cc. of blood was transferred, after removing the needle from the syringe, to each of two 10 by 75 mm. test tubes, which were placed at once in a water bath, maintained at 37.5±2°C. After standing 3 minutes the tubes were tilted simultaneously and gently to a uniform angle of 90° at ½ minute intervals. The end point was assumed to have been reached when the tubes could be held in an inverted position for 15 seconds without disrupting the clot. The interval from the entry of the blood into the syringe to the end point was recorded as the clotting time for each tube, and the results averaged to the nearest ¼ of a minute. The error of this method was approximately 10%.

Prothrombin Time: The technique employed was a combination of modifications of the original Quick procedure.[10] All estimations were done in duplicate (and, when deemed advisable, in triplicate or quadruplicate) on a 5% dilution of the plasma sample.

The diluent used was a portion of the patient's own plasma rendered prothrombin-free with a 30% suspension of barium sulphate (barium plasma), according to the technique of Tanturi and Banfi.[13] A commercial thromboplastin (Difco) was used in preparation of thromboplastin emulsion which was frozen and stored as suggested by Fuller.[5] The emulsion was prepared in bulk by suspending contents of 200 ampules (30 gm.) in 500 cc. of oxalated saline, incubating at 50°C., for 15 minutes with only occasional agitation; and separation of the coarser particles by filtration through cotton and gauze. The filtrate was apportioned in 1 to 3 cc. amounts in small test tubes, which were then stoppered and frozen.

Shortly before use, a tube of the frozen extract was removed, thawed at 37.5° in the water bath, and mixed with an equal volume of 0.02 M calcium chloride. After having reached the temperature of the water bath, 0.2 cc. of this mixture was blown from a micropipette into a 10 by 75 mm. tube containing 0.1 cc. of the 5% plasma, also at 37.5°C. The end point was distinct and easily detected by lifting the adherent clot out of the solution with a small nichrome wire loop.

Statistical Analysis. All mean differences obtained from the data were subjected to statistical computation by the methods of Fisher.[4] Differences are considered "significant" when the probability is less than 5 in 100 that chance would account for the result. When the critical ratio (CR) exceeds the 't' value obtained from the Fisher 't' tables, the difference is significant.

TABLE 2.–BLOOD CLOTTING TIMES AND BLOOD PROTHROMBIN TIMES IN NORMAL AND TUBERCULOUS PATIENTS

A. Blood Clotting Times

	Normal	Tuberculosis
No. of Cases	26	20
Mean (Minutes)	7.75*	8.00*
Standard Deviation	1.4	0.95

* Statistical Analysis of Difference of Means
t (from Fisher 't' table) = 2.00
Critical Ratio (CR) = 0.69 (not significant)

B. Blood Prothrombin Times

	Normal	Tuberculosis
No. of Cases	16	11
Mean (Seconds)	35.2	35.2
Standard Deviation	2.6	3.1

Results. *Blood Clotting and Prothrombin Times of Normals and of Tuberculous Controls.* The results are summarized in Tables 2 A & B. These findings are in agreement with the few reports quoted by Muller[7] that the blood clotting time is unaffected in tuberculosis. The mean prothrombin time of 5% plasma in the normal and tubercular groups was identical. This series is too small to permit generalizations but tends to support the view of Poulsen and Plum[8] that phthisis has no appreciable effect on the prothrombin time. Analysis of our data revealed no correlation of the clotting

time or prothrombin time with age, activity or extent of the lesion in either the control or streptomycin group.

Serial Clotting Times. The means of the blood clotting times obtained serially and their standard deviations are recorded in Table 3. The significance of the mean differences between the various test periods is revealed by the statistical analyses of Table 4.

TABLE 3.–SERIAL MEAN BLOOD CLOTTING TIMES (IN MINUTES) OF CONTROL GROUP AND TUBERCULOUS PATIENTS INJECTED WITH STREPTOMYCIN

	13 Streptomycin Patients					13 Control Patients				
		Minutes after Streptomycin					Minutes after Distilled Water			
	Before Injection	15	45	90		Before Injection	15	45	90
	7.75	6.75	8.5	8.75		7.5	7.5	8.0	7.0
Standard Deviation	0.99	0.84	1.62	1.06	Standard Deviation	1.03	1.36	1.12	0.83

TABLE 4.–STATISTICAL ANALYSIS OF MEAN DIFFERENCES OF SERIAL BLOOD CLOTTING TIMES

Intervals Being Compared	Diff. of Means* in Minutes	SD**	CR***	t****
A. Within Streptomycin Group				
Before – 15′ after	−1.00	0.36	**2.77**	2.056
Before – 45′ after	+0.75	1.78	0.42	2.056
Before – 90′ after	+1.00	0.40	**2.56**	2.056
15′ – 45′ after	+1.75	0.50	**3.50**	2.056
15′ – 90′ after	+2.00	0.38	**5.29**	2.056
45′ – 90′ after	+0.25	0.53	0.47	2.056
B. Within Control Group				
	0.0	0.48	0.0	2.056
Before – 45′ after	+0.5	0.42	1.19	2.056
Before – 90′ after	−0.5	0.37	1.36	2.056
15′ – 45′ after	+0.5	0.55	0.92	2.056
15′ – 90′ after	−0.5	0.45	1.11	2,056
45′ – 90′ after	−1.0	0.39	**2.56**	2.056
C. Between Control and Streptomycin Groups				
Before Injections	+0.25	0.39	0.64	2.056
15′ after	−0.75	0.45	1.67	2.056
45′ after	+0.50	0.54	0.93	2.056
90′ after	+1.75	0.38	**4.60**	2.056

* In A & B plus sign (+) indicates increase from period before to period after, minus sign (−) indicates decrease; in C, plus sign (+) indicates increase in streptomycin, over control group; the minus sign (—) the reverse.

** SD=Standard Error of Difference

*** CR=Critical Ratio; bold-face figures are significant.

**** t=Obtained from Fisher 't' table.[4]

It will be noted that there is a significant decrease in the 15 minute period. From this it might appear that there is an increase in coagulability after streptomycin. However, it will be noted that there is also a significant increase of one minute in the 90 minute period after streptomycin as well as increases between the 15 and 45, and 15 and 90 minute periods. This may, with equal justification, be interpreted as indicating a decline in coagulability. It is, of course, conceivable that streptomycin may be responsible for both effects, but when one turns to the control group (B), it is observed that there is a significant decrease in clotting time from the 45 minute to the 90 minute period. Since streptomycin obviously cannot be responsible for this decrease in the control group, it would be unwarranted to hold it ac-

countable for the similar change in the streptomycin group.

On the other hand, one cannot entirely exclude the possibility that streptomycin may cause the increase noted in the 90 minute period, particularly, since no such significant increase is found in the control group. Moreover, there is a rather significant increase of 1.75 minutes (CR equals 4.60) when comparison is made between the 90 minute periods of the control and streptomycin group (Table 4 C). However, there are no significant increases, when the 15 minute and 45 minute periods of both groups are compared. Thus, the meaning of the isolated increase in the 90 minute period of the streptomycin, over the control group becomes problematical.

TABLE 5.—SERIAL MEAN PROTHROMBIN TIMES* OF CONTROL GROUP AND OF TUBERCULOUS PATIENTS INJECTED WITH STREPTOMYCIN

	13 Streptomycin Patients				13 Control Patients			
		Minutes after Streptomycin				Minutes after Distilled Water		
	Before Injection	15	45	90	Before Injection	15	45	90
	42.7	42.8	42.7	41.7	41.5	42.4	40.5	41.9
Standard Deviation	2.96	3.30	3.14	3.20	5.63	4.93	3.68	5.93

* of 5% plasma in seconds

Serial Prothrombin Times. The means of the prothrombin time for the separate test periods and their standard deviations are presented in Table 5. Statistical analysis of the mean differences reveals no significant differences within or between the 2 groups.

Blood Clotting Times and Prothrombin Times Obtained on Different Days. The composite results are shown in Tables 6 and 7. No significant differences can be demonstrated between the mean prothrombin times or the mean clotting times of the streptomycin and control groups.

Discussion. Although serial blood clotting times following streptomycin show some significant differences, these are too indeterminate to ascribe them unconditionally to its action. The limited amount of data, as well as the possible existence of other unknown factors which may influence them, makes it necessary, that any differences found within the streptomycin group, or between the streptomycin and control groups, significant though they be statistically, be consistent and unequivocal before attributing them to streptomycin rather than to some other unknown variable. However, while not conclusive, the data (Table 4) *suggest* that streptomycin exerts an anticoagulant effect.

From the blood clotting times obtained on different days no effect of streptomycin is discernible. It should be emphasized that the comparisons made by this method of study are of grosser nature. Averages obtained for 2 hour periods are being compared. Differences may occur within this period which are obliterated by the process of averaging. Hence, the failure to detect any effect by this method does not necessarily imply that the differences noted in the serial study cannot be attributed to the action of the antibiotic.

The results of the prothrombin time studies both serially and on different days indicate that streptomycin exerts no demonstrable effect on the prothrombin time.

Macht's[6] demonstration of the decided thromboplastic action of streptomycin in rabbits and cats was not duplicated in these studies in man. The lack of effect cannot be attributed to insufficient dosage. Macht employed

total dosages ranging from 1 to a maximum of 5 mg. per animal, a level not likely to exceed the average injected dose 7.56 mg. per kg. used in our patients. Differences of species or of technique may, of course, be responsible.

Another possibility which cannot be adequately eliminated is that the tuberculous process itself may have masked or interfered with the response to streptomycin. A thorough search of the literature yields no positive information on this point. On clinical grounds, it is quite improbable that such is the case. The essentially normal levels of blood clotting and prothrombin activity found in our patients, as well as by others,[7,8] would seem to indicate that the physiological mechanisms involved in regulating these functions are normal in tuberculosis, and hence can be expected to respond normally to the action of coagulant or anticoagulant agents. It would be necessary, however, to restudy the effects of streptomycin in normal, healthy individuals to be certain that tuberculosis does not affect the response.

TABLE 6.—COMPARISON OF MEAN BLOOD CLOTTING TIMES OF STREPTOMYCIN PATIENTS AND OF CONTROLS, PERFORMED ON DIFFERENT DAYS

14 Streptomycin Patients		11 Control Patients	
	Mean Clotting Times in Minutes		Mean Clotting Times in Minutes
	8.75*		8.5*
Standard Deviation	1.26	Standard Deviation	0.3

* Statistical analysis of Difference of Means: t (from Fisher 't' table)=2.06; CR=0.54 (not significant).

TABLE 7.—COMPARISON OF MEAN PROTHROMBIN TIMES OF STREPTOMYCIN PATIENTS AND OF CONTROLS, PERFORMED ON DIFFERENT DAYS

14 Streptomycin Patients		12 Control Patients	
	Mean Prothrombin Time in Seconds		Mean Prothrombin Time in Seconds
	36.1*		37.5*
Standard Deviation	2.87	Standard Deviation	3.7

* Statistical analysis of Difference of Means: t (from Fisher 't' table)=2.05; CR=1.08 (not significant).

Summary and Conclusion. 1. The effects of streptomycin on the blood clotting and prothrombin times of 21 patients with pulmonary tuberculosis were studied by modifications of the Lee-White and Quick techniques. A parallel series of 21 phthisic patients served as controls. Two methods of investigation were used: (a) tests during the same hours on different days; (b) serial tests during a 90 minute period immediately after the injection of streptomycin.

2. No correlation between the age, activity, or extent of the tuberculosis, and the clotting or prothrombin times was found in either the control or streptomycin groups.

3. No significant effects upon the prothrombin time could be demonstrated by either method of investigation.

4. Significant differences between the mean clotting times of some of the test periods were obtained by the serial method, but the results were inconclusive and could not be ascribed with certainty to the influence of streptomycin. No significant differences were detected between the mean clotting times of the streptomycin and control group by the "different day" method of study.

5. Although there are no clinical grounds for believing that tuberculosis would affect the behavior of the clotting and prothrombin times in response to streptomycin, this possibility cannot be excluded in this study.

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THE CONTROL OF DICUMAROL THERAPY*

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With the increasing use of dicumarol in the prophylactic and active treatment of thrombo-embolic conditions, the control of its administration and effects becomes increasingly important.

According to the present concept the chief effect of the drug is the depression of the plasma prothrombin, and on this basis a diminution in the clotting tendency of the blood. Several investigators[5,19,28] have found that the adhesiveness of the platelets is less in dicumarolized blood than in normal controls, suggesting a second factor by which the drug may produce an anticlotting effect. The chief effort in the control of the administration of the drug, however, has been directed towards the maintenance of the plasma prothrombin at a level at which intravascular clotting will not occur and yet bleeding is not induced. In order to achieve this most workers in the field have employed the "one-stage" prothrombin determination described by Quick[14] or various modifications of it.

By diluting normal plasma to various concentrations, Quick set up percentage values of prothrombin corresponding to the clotting times of the various dilutions. Because of variations in the activity of thromboplastin solutions prepared in various laboratories, this percentage scale could not be used by all investigators, and rather than set up a separate scale each time a new lot of thromboplastin is prepared as urged by Allen,[1] many workers choose to report prothrombin levels in terms of the clotting times or "prothrombin time." Campbell, *et al.*[6] and Link[12] and his co-workers found that diluting plasma to 12.5% of normal before determing its "prothrombin time" resulted in a more sensitive reflection of variations in the prothrombin level.

The one-stage method utilizes an excess of thromboplastin, an optimum amount of calcium, and a constant temperature to render the clotting process more uniform. The normal buffering action of the plasma also serves well to maintain a satisfactory pH range, and the blood colloids probably serve further to stabilize the reaction. There are numbers of known factors, however, and no doubt some as yet unknown, which are left uncontrolled and may be the cause of wide variations in expected prothrombin estimates by the one-stage method.

Among the known variables are differences in the rate at which prothrombin is converted to thrombin. This varies from species to species and often among individuals of the same species.[17,25,26] Fantl and Nance[8] suggested that normal coagulation depends not only on a normal prothrombin but on a prothrombin accelerator as well. Ware, Guest, and Seegers[22,23] have recently isolated a plasma fraction which has such a property and suggest that it may be an important factor in certain pathologic blood clotting tendencies.

It has been known for some years that normal human serum contains a

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factor which neutralizes the active principle in placental toxin. Recently Schneider[16] has suggested that the toxic factor may be thromboplastin and its inactivator antithromboplastin. He presents evidence to indicate that this latter factor is increased during pregnancy. In what other clinical conditions it may vary and what role, if any, it may play in influencing the clotting time in the one-stage prothrombin determination is unknown.

Antithrombin may vary widely in different plasmas,[13] and variations in the heparin content of blood have been observed.[3,4] The catalytic action of heparin on antithrombin[18] may be of real clinical importance in patients with abnormal heparin levels.

Fibrinogen levels are known to vary under certain conditions[9,10,21] though Witts[27] found that the plasma fibrinogen must fall to less than 30% of normal before it materially affects the "prothrombin time." Fibrinogen changes in dogs given dicumarol have been reported.[11]

The results of the one-stage prothrombin determination then may be influenced by one or more of the above mentioned factors and possibly others as yet unknown. Diluting the plasma to 12.5% or less before the determination is made may modify the influence of these factors to some extent:

The "two-stage" determination as described by Warner, Brinkhous and Smith,[24] by utilizing the two-stages in which blood normally clots, eliminates certain of the above mentioned factors, namely, the variation in the conversion rate of prothrombin and variations in the plasma fibrinogen. By providing for high dilution of the plasma, it neutralizes the antithrombin factor. Heparin may affect both the one-stage and two-stage tests in that it interferes with the conversion of prothrombin to thrombin. Antithromboplastin is highly sensitive to dilution,[13] and diluting the plasma in the two-stage determination renders that factor inactive during the procedure.

The important consideration in the control of dicumarol therapy is the maintenance of a safe, effective level of plasma prothrombin. A safe level has been taken to be that at which bleeding does not occur. The importance of this is emphasized by the reports of fatal hemorrhages during its administration. The possible deleterious effects of the drug administered over a period of years have not been determined. The effective therapeutic level for the prevention of intravascular clotting, or the extension of clots already formed, has not been definitely established, and there is at present no evidence that there is a therapeutic level at which intravascular clotting can absolutely be prevented. Several investigators[7,15,20] have reported a lowering of the incidence of experimentally produced thrombi in dicumarolized animals as compared to control series, and there are numerous clinical reports of a lowered incidence of post operative thrombo-embolism in patients given dicumarol prophylactically. Allen[2] recommends a therapeutic range of between 10 and 30% using the one-stage method for prothrombin determination. He has observed that intravascular clotting rarely occurs when the prothrombin level is less than 30% of normal, and bleeding is rare when the prothrombin is above 10%.

Present Study. The purpose of the present study was to establish, if possible, a safe effective level at which the prothrombin can be maintained over an indefinite period of time, and to determine the methods best suited for such maintenance. Since the present confused state of terminology makes it difficult to know the effective level, it seemed reasonable to maintain the prothrombin in the lowest bracket which proved to be safe, thus allowing the utmost benefit from the drug. Previous experience in this laboratory with the

use of both the two-stage and the one-stage methods has shown the former to be more sensitive in reflecting changes in the plasma prothrombin.

This report represents a study of 99 patients under dicumarol therapy. In 91 of the cases, both the orthodox Quick test[14] and the two-stage test were used. The thromboplastin in the Quick test in all instances gave a normal control clotting time of 11 to 12 seconds. In 14 cases, the modification of the Quick technique, as suggested by Campbell and his associates;[6] that is, the "12.5% plasma" technique was used. In these cases the same test was made on 5% plasma to see if the use of a still more dilute plasma would result in more sensitive changes. The shortest period of administration of the drug was 4 days and the longest 23 months. The average time was 60 days, though the several prolonged periods bring this average to a somewhat higher figure than the usual period of therapy. Four to 6 weeks have been the arbitrarily established period for the usual case of acute thrombosis, this being extended if the individual case seemed to warrant it.

Method of Administration. When the patient is first seen a prothrombin determination is made, and if it is found to be above 80% (two-stage), an initial dose of 300 to 500 mg. of dicumarol, depending on the size of the patient and the original prothrombin level, is given. The second day 100 to 200 mg. are given. Prothrombin determinations are repeated 2 days after the initial dose, and the selection of subsequent dosages is based on the prevailing prothrombin levels. At the present time determinations are made before the initial dose of dicumarol, 48 and 72 hours after that dose, and then at intervals of 2 days until the prothrombin drops to therapeutic levels. This usually requires 3 to 7 days but may take longer. Determinations may then be reduced to twice weekly, later on to once a week. As will be discussed later, a bracket of between 10 and 20% plasma prothrombin (two-stage) is regarded as ideal in each case but is difficult to maintain. In most cases, however, variations over a period of time may be limited to between 5 and 35%. In hypertensive patients, an effort is made to keep the level in the neighborhood of 30%. When the prothrombin drops below 5%, as frequently happens in the early days of treatment, a urine specimen is examined daily for blood. The drug is not withdrawn and usually vitamin K is not given. The dose of dicumarol is reduced by 50 mg. for 1 or 2 days, depending on the prothrombin determinations, which are usually one daily or every 2nd day during this period. Usually the prothrombin returns to a level above 10% in a few days. Efforts are directed towards anticipating this rise and stopping it at the desired level. Bleeding is not necessarily expected at such low levels, but if it occurs the same procedure is followed. The one-stage test is of particular value at this point. If it shows a level of 10% or below, the safety margin supplied by the other blood clotting factors is known to be reduced and bleeding may be imminent. (Fig. 5). If a patient leaves the city for several weeks at a time, he continues to take dicumarol and sends samples of blood in at 7 to 10 day intervals. During weather other than that of hot summer days, the prothrombin is relatively stable in transit. From nearly any section of the country it can reach the laboratory within 15 hours from the time it is drawn. The common maintenance dose over a long period of time is 300 to 450 mg. per week, though patients may require greater or lesser quantities of the drug.

Combined Use of Heparin and Dicumarol. In 34 of the acute cases of intravascular clotting, heparin was used in the first 48 to 72 hours before the full effects of dicumarol could be expected. A discussion of heparin therapy is outside the scope of this paper, but it must be borne in mind that heparin interferes with the conversion of prothrombin to thrombin, and any blood sample intended to guide the dosage of dicumarol must be drawn after the effects of heparin have been expended.

Comparsion of Methods. With the use of the two-stage test it has been possible in most instances to reduce the prothrombin level to a bracket of between 5 and 35% and, with an occasional level slightly below or above, hold it between these two levels. Figures 1, 2 and 3 are representative charts of patients easily controlled under di-

cumarol therapy, with little variation in dosage once a therapeutic level has been reached. In Figs. 1 and 2, one-stage, whole plasma, determinations are shown for comparsion with two-stage readings. Figs. 3 and 4 show, in addition, the results of "prothrombin times" on 12.5% plasma. In many instances the prothrombin variations as measured by the different methods sometimes fatal hemorrhages have occurred. The two-stage test, however, shows that the prothrombin has not varied greatly from the previous level, and no marked change in the dicumarol dosage was made. At the time of the next test, the results of the one-stage and the two-stage were again parallel. The reason for the marked variation of the one-stage in such instances is not

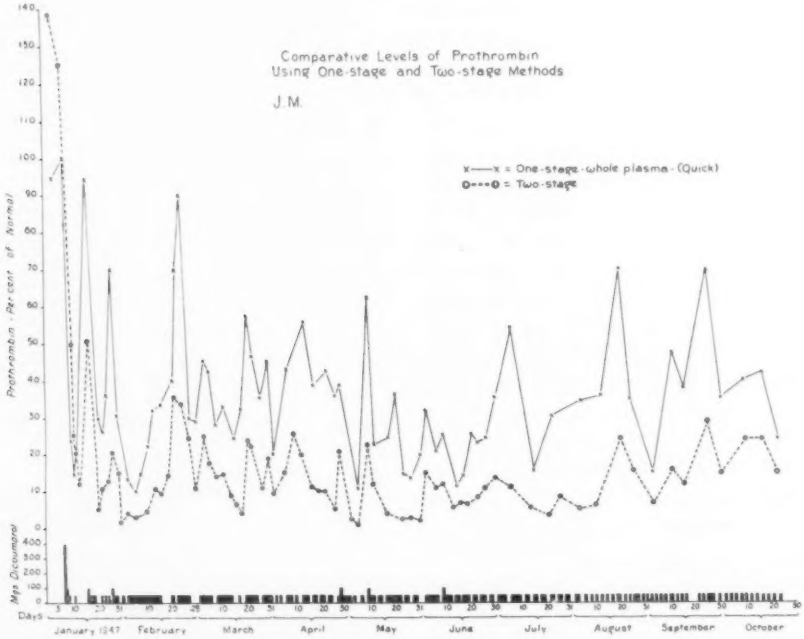

FIG. 1.—Comparative prothrombin levels, 1-stage and 2-stage methods, of a patient receiving dicumarol for 10 months. She was originally treated for a thrombophlebitis, and because she felt her multiple sclerosis was improved during the therapy, her physician maintained it for 10 months. Note the wide variation between the 1-stage and 2-stage prothrombin readings. Her sensitivity to dicumarol was determined while she was hospitalized during the early days of her thrombophlebitis, and she was later treated as an outpatient. There was no apparent objective improvement in her multiple sclerosis.

parallel each other, but this parallel is not consistent. For example, in Fig. 1 in several instances the two-stage method shows a level of between 20 and 30%, while the one-stage registers a level of between 60 and 70%. If the one-stage test were guiding the therapy, one would be prompted at such points to give a large dose of dicumarol which would likely lower the prothrombin to a dangerous level. In all probability it is in such instances that serious and entirely clear, but one or more of the factors mentioned earlier may have been responsible. Likewise, the prothrombin estimates using 12.5% plasma do not show a uniform variation as compared to the two-stage or even the one-stage whole plasma determination (Figs. 3 and 4). Five % plasma was no more uniform than the 12.5% in reflecting prothrombin variations.

As mentioned above, 91 of the 99 cases were followed with both the one-

stage and two-stage tests. Most of the other 8 cases were at times checked with the one-stage as well as the two-stage determination, particularly when the prothrombin level fell to less than 10%. This was of value in estimating the summation of the various clotting and anti-clotting factors of the individual blood at a point where the patient might be in danger of hemorrhage from a prothrombin deficiency. and an elevation of the prothrombin by diminution of the dosage or withdrawal of the drug or, in some instances, administration of vitamin K is indicated (Fig. 5).

Bleeding Hazard. Bleeding occurred in 15 cases, the most common site being the urinary tract. In 13 of the 15 patients, the prothrombin level was between 1 and 11% (two-stage) when the bleeding became apparent, and

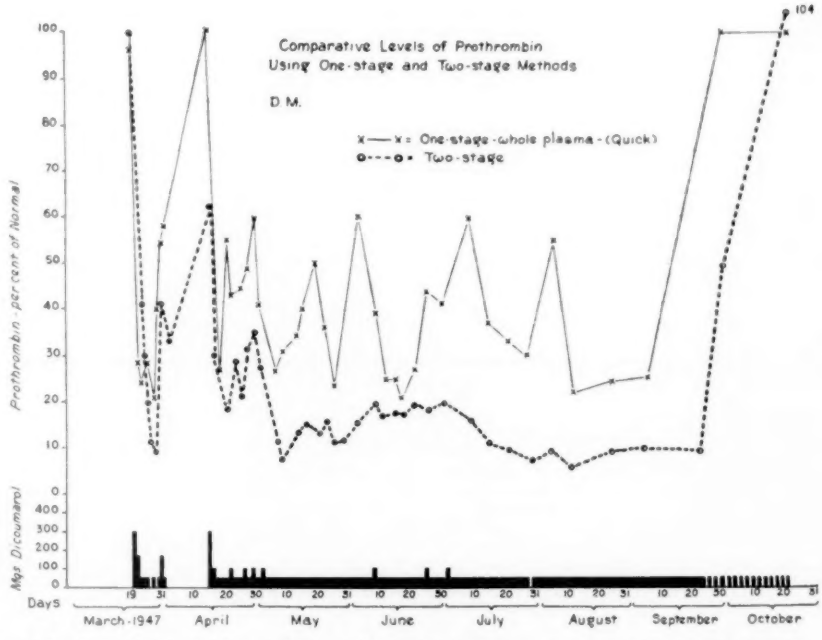

FIG. 2.—Prothrombin levels of a patient on dicumarol therapy, easily controlled for months with weekly prothrombin determinations. A phlebothrombosis developed following minor injury to the leg, and the patient improved on heparin and dicumarol. He left the hospital after 12 days and therapy was discontinued. Symptoms recurred 2 weeks later, and heparin and dicumarol were re-instituted. A thrombus in the great saphenous vein remained palpable and somewhat tender over the ensuing 5 months, during which his his prothrombin was maintained within a bracket of 7 and 19%. On 3 occasions the prothrombin according to the 2-stage method stood at 15, 16 and 9% respectively, while the 1-stage whole plasma test showed levels of 60, 59 and 55% respectively. There was no bleeding at any time and no residual signs or symptoms after therapy was stopped.

Even though this prothrombin as measured by the two-stage method might stand at 4%, a one-stage determination showing 10% or more would indicate that there were sufficient compensating factors to make bleeding unlikely (Fig. 3). On the other hand, a level of less than 10% of both methods is a warning that bleeding may be imminent, stopped when the prothrombin rose to between 15 and 20%. In the other 2 cases bleeding followed trauma, the prothrombin being 36% at the time in both patients. In 13 cases bleeding stopped following reduction of the dosage of dicumarol. Two patients received vitamin K to raise the prothrombin level. Three patients with levels of be-

tween 5 and 20% have fallen without sustaining bruises. There was no instance of fatal hemorrhage in this series.

Seven patients have been on controlled therapy during menstruation, 5 of them having had prothrombin levels between 5 and 25% at the time. In one case, the menstrual period was one day longer than usual. The intensity of bleeding was not changed. Five patients noticed no variation from the

the prothrombin is above 50%, it does occur and may well have been a factor in this instance.

Effectiveness of Dicumarol Therapy. The effectiveness of dicumarol in preventing thrombosis or its complications is difficult to evaluate in that adequate controls cannot be conveniently set up.

In this series it was used as a prophylactic measure in 12 cases. Of the 12 cases, 1 developed thrombophlebitis

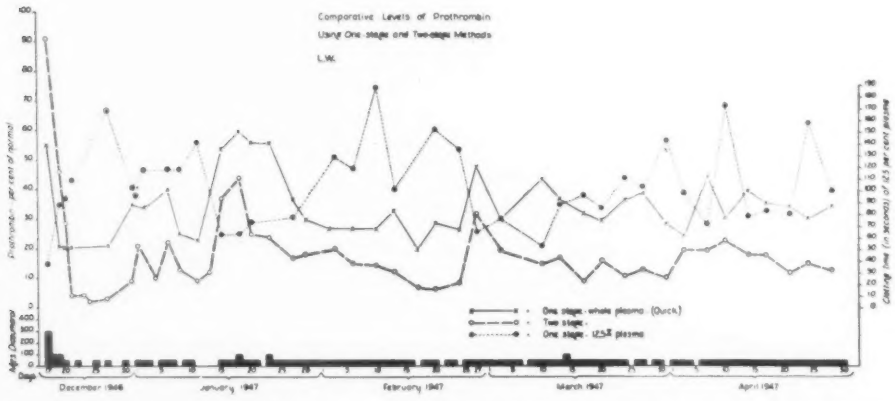

FIG. 3.—Prothrombin levels of a patient under dicumarol therapy because of an acute, severe thrombophlebitis of the right leg. The results of the whole plasma techniques (1-stage and 2-stage) are expressed in per cent of normal on the left hand, and the results of the 12.5% plasma are recorded in seconds,—the right hand ordinate. In the early stages, the results of the 1-stage whole plasma technique closely parallel at a somewhat higher level those of the 2-stage test. Later, this parallel disappears, the 1-stage showing a rise, while the 2-stage shows a drop in prothrombin level. The prothrombin time of 12.5% plasma in general shows a rise when the prothrombin level according to the whole plasma 1-stage test falls, but the timings are erratic and not suitable for dicumarol therapy control. Note that while on December 21 the prothrombin, 2-stage, fell to 2% of normal, the 1-stage test showed a 20% level, indicating that there were sufficient compensating factors in the blood to prevent bleeding. The patient did not develop bleeding during his course of therapy.

normal. One patient developed microscopic hematuria when her prothrombin was 7%. It had stopped 2 days later when the prothrombin reached 24%. Five days after this, she began to menstruate excessively. Her prothrombin level was 53% at the time. During the next 60 hours she was given 24 mg. of vitamin K parenterally by her physician. Excessive bleeding had stopped by the time the vitamin was started. Three days after the last dose her prothrombin level was 87%. Such excessive bleeding was out of the ordinary for this patient, and while it is unusual for bleeding to be present when

postoperatively. She was uncooperative and administration of the dicumarol was not satisfactory. When her thrombosis occurred, the prothrombin level was 66%. No sign of thrombosis occurred in the other 11 cases.

Twenty-one cases of acute coronary thrombosis were dicumarolized. There were no deaths, and none developed other thrombo-embolic phenomena. One patient with myocardial decompensation, who earlier had had anterior and posterior myocardial infarctions, was treated with dicumarol after he developed phlebothrombosis of the left leg and signs of a small pulmonary

embolus. Before his prothrombin reached therapeutic levels, signs of thrombosis developed in the other leg. Swelling of both legs disappeared after 2 weeks, no further emboli developed, cardiac function improved, anticoagulant therapy was discontinued and the patient left the hospital. Sixteen days after the last dose of dicumarol, he developed a thrombus of the right femoral vein, and 4 days later of the left. He died suddenly 2 weeks later of what appeared to be a cerebral embolus. He had had no dicumarol for 34 days.

Acute thrombophlebitis or phlebothrombosis of the lower extremity without signs of embolism were treated with anticoagulant therapy in 43 instances. Papaverine was used in a few cases, but the treatment otherwise was bed rest. The legs were not elevated or immobilized. One case of acute thrombophlebitis of the abdominal wall veins was treated likewise. The patients were kept in bed until the swelling disap-

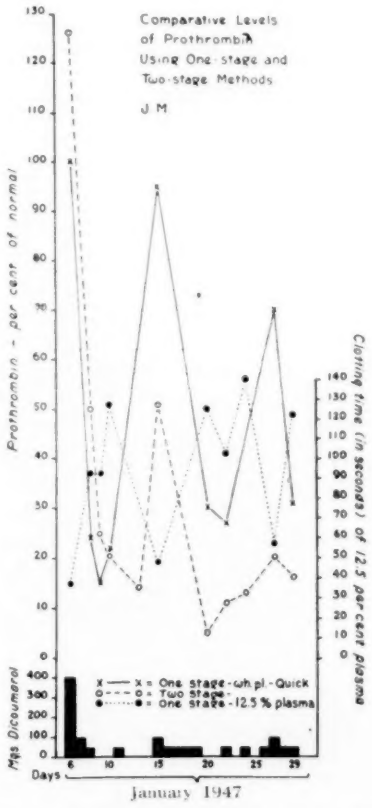
Comparative Levels of Prothrombin Using One-stage and Two-stage Methods
J M
Prothrombin - per cent of normal
Clotting time (in seconds) of 12.5 per cent plasma
Mgs. Dicoumarol
X —— X = One stage - wh. pl. - Quick
O - - - O = Two stage
● ····· ● = One stage - 12.5 % plasma
Days
6
10
15
20
25
29
January 1947

FIG. 4.—Comparative prothrombin levels according to the 1-stage whole plasma technique, the same technique using 12.5% plasma and the 2-stage technique. The results of the whole plasma techniques (1-stage and 2-stage) are expressed in per cent of normal, on the left hand, and the results of the 12.5% plasma method are expressed in seconds,—right hand ordinate. Note that on January 6, 15 and 27 the "prothrombin time" of the 12.5% plasma is 37, 48 and 57 seconds, respectively, relatively near one another. The 2-stage method at these points shows a level of 126, 51 and 20% respectively, relatively divergent values. This chart represents the first month of treatment of the patient shown in Fig 1, and as will be noted there, her prothrombin (2-stage) remained fairly well stabilized over a period of time. Attempts to order dicumarol on the basis of the 1-stage method using either whole or 12.5% plasma might have led to undesirable and serious results.

peared in the instances of phlebothrombosis, and until the pain and redness were gone in the thrombophlebitis cases. There were no instances of embolism. Three cases of thrombophlebitis of only the superficial veins at the time anticoagulant therapy was started did not progress to involvement of the tient a sizable optico-ciliary anastomosis was observed after 8 months of dicumarol therapy.

Thirteen cases of embolism, single and multiple, were treated in patients with phlebothrombosis (8), auricular fibrillation (3), bacterial endocarditis (1) and no definitely known source of

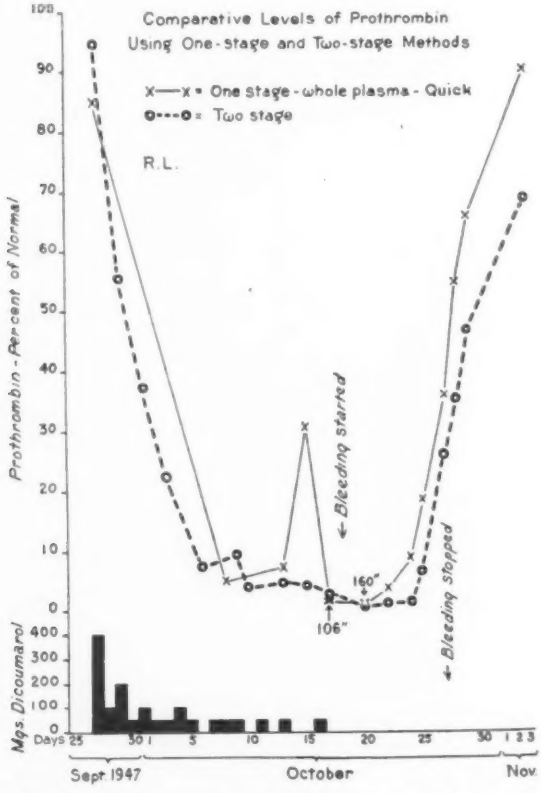

FIG. 5.—Rapid response to dicumarol in a patient relatively sensitive to the drug, and a prolonged bleeding despite withdrawal of the anticoagulant. The 50 mg. dose of dicumarol was given on October 16 by error and gross hematuria, was observed on October 17. Bleeding continued and the prothrombin level showed little change until October 25. On October 26, because of troublesome dysuria, 3 doses of 19.2 mg. each of Hykinone were given intravenously at intervals of 2 hours. Bleeding stopped the following day.

deep veins. None of the cases of phlebothrombosis developed into thrombophlebitis.

Ten cases of thrombosis of the central retinal vein were given dicumarol, 2 of them receiving heparin as well. There was no progression of the loss of vision in any case, and improvement occurred in all cases. In one pa- the emboli (1). In 11 cases there were no further emboli as long as the patients stayed on treatment. One patient, controlled with difficulty, had repeated small pulmonary emboli from what was considered to be a mural thrombus in the heart. Two of these developed when her prothrombin was at 11 and 44% respectively, and a phle-

bothrombosis of the left leg came on when her prothrombin was 79%. What was clinically a splenic infarct developed when the prothrombin was 10. Another patient had what appeared to be repeated small pulmonary emboli when his prothrombin was 34%. No further ones occurred when it dropped to 26% or below.

One patient with Parkinson's disease was treated with dicumarol over a period of 42 days without apparent benefit.

Four cases of multiple sclerosis were treated with dicumarol therapy, one for as long as 11 months. Three showed no improvement, and the other who is still on therapy at the writing of this paper has shown subjective improvement.

Three patients with cerebral thrombosis were treated with dicumarol. One, a man of 68, had 2 episodes of paralysis in 2 years. He was placed on dicumarol therapy following the first attack and completely recovered. Two years later he had a recurrence and was again placed on dicumarol therapy. Recovery was again complete, and he has been on dicumarol therapy since that time, a total period of 23 months. He has had no recurrence. A second patient, a man of 82, improved following his cerebral accident and left the hospital after 7 days. Dicumarol was discontinued 6 days following this. Six months later he again developed cerebral thrombosis and was again placed on heparin and dicumarol. His condition again improved, and he was discharged after 55 days without continuation of therapy at home. Six weeks later he died suddenly, and at autopsy a large pulmonary embolus and phlebothrombosis of the right hypogastric vein were found. Permission to examine the head was not obtained. A third patient, a woman of 74, has shown steady improvement after 6 weeks of dicumarol therapy following cerebral thrombosis.

This series of cases is too small to be a basis for conclusion as to the value of dicumarol as a therapeutic and prophylactic agent. However, of the 99 cases included here, 94 were treated actively or prophylactically for thrombotic or thrombo-embolic conditions. Of these, three (3.3%) had further thrombo-embolic phenomena while on dicumarol, 1 while under what was considered to be adequately controlled therapy. The other 2 were not satisfactorily controlled when the thrombus or embolus developed. The results support the work of others who have reported a decrease in thrombo-embolic phenomena in patients receiving this type of treatment.

Prolonged Dicumarol Administration. In this series, 6 patients received dicumarol longer than 4 months, 4 for over 6 months, 3 for more than 9 months, 2 for 12 months, another longer than 20 months, and one patient took it for over 23 months. They were controlled by tests at weekly intervals, and in the long term cases the intervals were as long as 2 weeks.

Neither these nor any of the other patients under treatment for shorter periods of time, showed any signs of toxic reaction to the drug. Occasionally, a patient vomited when large doses—300 to 400 mg.—were taken at one time.

It is of interest that one patient in this study required as little as 100 mg. of dicumarol weekly as a maintenance dose, while one received as high as 2800 mg. a week without being adequately controlled. The factors influencing these wide variations in tolerance to the drug are not clear. The influence of drugs such as the methylxanthine will be discussed in a later paper.

Summary and Conclusions. 1. Ninety-nine patients were treated actively or prophylactically with dicumarol, and in 34 cases heparin was also used.

2. With the use of the two-stage prothrombin determination, it was possible accurately to maintain the prothrombin level within a desired range over a period of months, with a maximum variation in some instances of 15%.

3. Fifty (50.5%) of the cases were treated as outpatients, most of them on weekly prothrombin determinations. The treatment period varied up to as long as 23 months. Some of the patients were out of the city for weeks at a time, and blood samples were sent to the laboratory for control purposes.

4. One-stage prothrombin methods (whole plasma, 12.5% and 5% plasma) were compared with the two-stage method. In all cases, there were wide variations between the methods used.

5. The two-stage method is regarded as a more accurate and a safer method for the control of dicumarol therapy than any of the other methods used. The one-stage method is of real value, however, in estimating the summation of the clotting factors in an individual blood, particularly at a time when the prothrombin as measured by the two-stage test is below 10%.

6. Bleeding occurred in 15 (15.1%) of the 99 cases given dicumarol. In 13 of the 15 patients, the prothrombin level was between 1 and 11% (two-stage) when the bleeding became apparent, and stopped when the prothrombin rose to between 15 and 20%. In the other 2 cases bleeding occurred following trauma, the prothrombin being 36% at the time in both patients. The urinary tract was the most common site of bleeding.

7. In those patients in whom bleeding developed, withdrawal of the drug for 1 or sometimes 2 days was sufficient in most cases to bring the prothrombin level to within safe limits. Since the dicumarol therapy was accurately controlled, the individual patient's prothrombin level was usually not far below his bleeding threshold. In two cases, vitamin K was given to raise the prothrombin level which responded promptly, and the bleeding stopped in less than 24 hours in both instances. There were no cases of fatal hemorrhage in this series.

8. Three (3.3%) of the 99 patients on dicumarol therapy showed evidence of further thrombo-embolism. Of these, 1 showed such evidence while the patient's prothrombin was considered within the therapeutic range. In the other cases, it was above that range. The results of this study support the conclusions of other workers in the field that the use of dicumarol is of value in the prophylactic and active treatment of thrombo-embolic conditions. The results also suggest that a range of 10 to 30% (two-stage) is a safe, efficient level for the maintenance of plasma prothrombin.

9. Other than bleeding, no toxic effects of dicumarol were observed. The prothrombin level promptly returned to normal when the drug was discontinued.

Miss Luellen Dale and Mrs. Angelina Vicencio contributed valuable technical assistance during this study.

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PROGNOSIS OF PNEUMONIA*

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There is a number of well known factors which have an influence on the prognosis of pneumonia, some of them are for good, others for evil. We wish to call attention to some of these factors.

Communities vary in the severity of their pneumonias, and in certain cities, Pittsburgh, for example, the death rate has always been known to be high: in fact, as compared with New York, almost double until very recent years after the introduction of chemotherapy.

In severe influenza epidemics, as in 1918, the prognosis of pneumonia is very much worse. In the winter of 1936-37 we had a small epidemic of rather virulent influenza with a subsequent rise in our pneumonia death rate.

There are some host factors which appear to have an evil influence on the outcome of pneumonia, namely, old age, chronic alcoholism, and neglect of the acute pneumonic infection after it has developed. Frequently, we see all of these factors combined in the same patient. It is our opinion that the last, the neglect of the pneumonia, is by far the most important and it is common experience to have in the pneumonia service patients with pneumonia who had been walking about the streets for a variable number of days. It is well to remember the pathologists' observation in this regard, namely, that at autopsy in cases of sudden death on the streets in the pneumonia season of the year, in about 15%, the cause of death is pneumonia. We usually have in each year a few patients who die within a few minutes to a very few hours after admission to the hospital. Such neglected cases have little importance as regards therapy, and it is misleading not to separate this group from those who have been available for treatment at least 24 hours in the hospital. Today very few, other than neglected cases of pneumococcic pneumonia, die.

The rate of the pulse we find to be the most reliable clinical sign as to the prognosis of the pneumonia. A gradually rising pulse rate to beyond 120 per minute is not good. The opposite also tends to hold true, namely, one rarely sees a fatal outcome in a pneumococcic pneumonia patient with a pulse rate consistently under 100. We do not include children in this group nor, of course, postoperative atelectasis.

The finding of pneumococci in the blood culture has always been in the past the most exact factor from which to make a prognosis,[1,9] but today penicillin cures many of the bacteremia cases which formerly died. The blood culture must be taken before any penicillin has been given because it does

* Read before the Association of American Physicians, Atlantic City, May 4, 1948.

not appear to take very much penicillin to change a positive to a negative culture. We would further emphasize the importance of making bedside blood agar plates so as to have bacterial colony counts. Over a period of a number of years we have yet to see a recovery from pneumonia where 15 or more colonies were counted on the plate from 1 cc. of blood made immediately at the bedside in cases where no specific treatment, serum or chemical, was given. In our opinion there is not much value in taking blood cultures in pneumonia if plates are not made. This is particularly true if one is studying any special form of therapy, as it makes the reading of the results of treatment easier and more accurate.

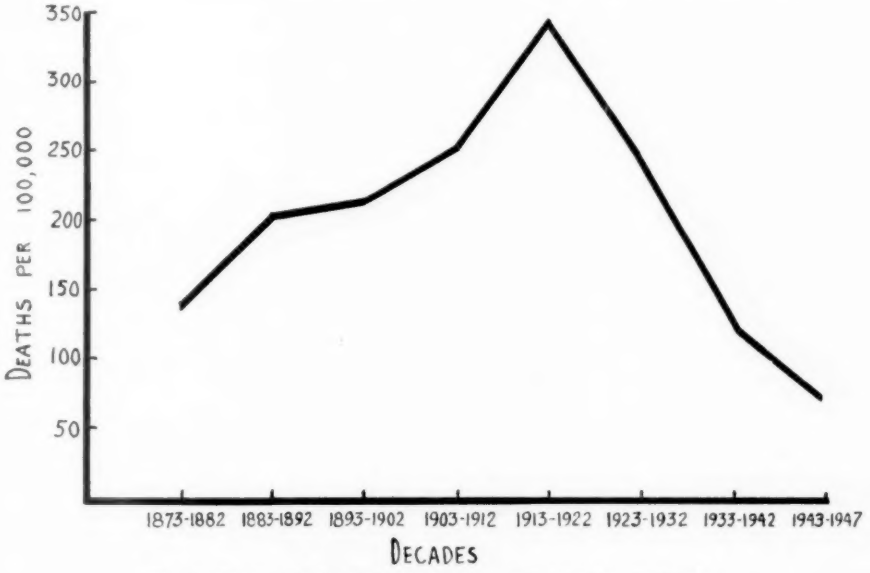

FIG. 1.—Pneumonia deaths in Pittsburgh. Average rates per decade.

A leukocyte count in pneumococcic pneumonia below 10,000 has usually carried with it a serious prognosis. However, in the past 21 months, 1946-48, this has not been true in our cases, as the following data from our records would indicate. In 1935-36 we had 81 cases with 18.7% of them showing a leukocyte count of 10,000 or less. The mortality was 61% in this small group of cases. They had a very high bacteremia rate of 46%. In our experience this was the rule in prognosis for pneumococcic pneumonia patients with low leukocyte counts. But during the past 21 months, 1946-48, the figures are very different. In this period we had 169 cases with 43.2% of them having leukocyte counts below 10,000, and a mortality of only 7%. The bacteremia incidence of the group was 34% which certainly is an index of the virulence of the infection. The low mortality we believe is due entirely to penicillin, but this does not alter the fact that in this large group of cases with low leukocyte counts a bad prognosis could not be made from the leukocyte count itself, and therefore, during the past 21 months the leukocyte count has had no prognostic value. The frequency of low leukocyte counts in pneumococcic pneumonia, in our opinion, is not due to the patient's

resistance, but to some unknown factor in the type of the infection. It has been noted by others,[6,8] in different parts of the country.

Finally, the most important influence for good on the prognosis of pneumonia today is penicillin. The following charts show some of these points on prognosis, particularly the results of treatment with penicillin.

Fig. 1 indicates a period of 75 years from 1873 to 1947. It is divided into 10 year periods except for the last one which is only 5 years. In each period the years are averaged. The chart is made from statistics from the Department of Health, Pittsburgh,[6] and represents the deaths from pneumonia per 100,000 population over this period of time. We would call attention to the first decade, 1873 to 1882, with the low figure of 139. Certainly, at that time there was no specific treatment for pneumonia, so the low mortality for that period must have been due to a milder infection. For the next 50 years, however, 1883 to 1932, the average year in each decade was never below 200. The great epidemic of influenza in 1918 accounts for the high peak of 343. From 1933 to 1942 there is a fall to 124 and for the last 5 years to 1947 the very low average figure for the year was 77. During the last 15 years the fall in the death rate has been defi-

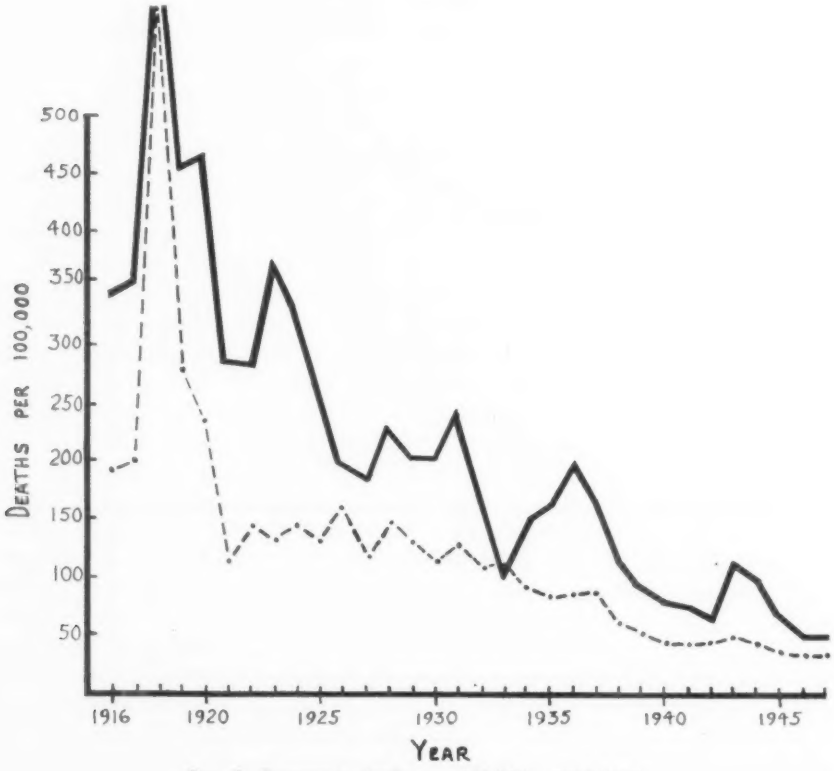

FIG. 2.—Pneumonia deaths per 100,000. 1916-1947.

nite. Serum was made more available by the City Health Department from about 1934 to 1938, and probably made some impression on the mortality figure. Sulfapyridine became available in 1939, and from that date on chemotherapy, including penicillin in the past

2 years, is chiefly responsible for the low mortality figure. However, in the early part of this last decade and a half, 1933 to 1938, the question of a milder infection may have to be considered as a possibility, since we do not believe that anti-pneumococcic serum was used widely enough to be entirely responsible for the fall in that period.

Fig. 2 indicates the difference in the pneumonia death rates in 2 communities, New York and Pittsburgh. The charts are made from statistics from the Department of Health of the 2 cities. Over a period of 32 years 1933 is the only year when our mortality rate was lower than New York, 105 to 108. Our pneumonia, in the clinical sense, was mild that year. There was, of course, no chemotherapy and not too much serum was used, as the City Health Department at that time was not supplying free serum for pneumonia cases. The low mortality figure in 1933, therefore, was spontaneous. In that year of the depression the Pittsburgh mills were not running and we had relatively little smoky atmosphere and much unemployment. We do not know exactly if these factors

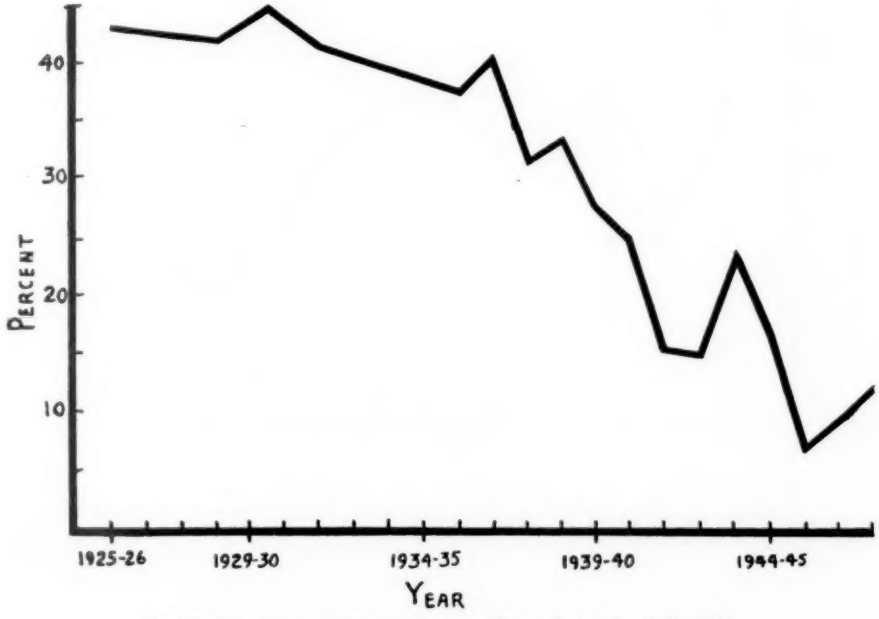

FIG. 3.—Mortality rate in pneumonia at Mercy Hospital. 1925-1948.

the death rate from pneumonia in Pittsburgh has always been higher than that of New York, except for one year. In the earlier years it was often double, but since chemotherapy the figures are more nearly equal. Our rates have dropped from 350 in 1916 to 54 in 1947, while the New York figure was 200 to 37. We wish to note the excessive peak in 1918 which was 1222 for Pittsburgh and 603 for New York; had any influence on the mortality rate of pneumonia. The rise in 1936-37 followed a sharp but small epidemic of influenza beginning Christmas week, 1936. From 1939 the sulfonamides had their influence on the curve and in 1945 penicillin was added. Probably in the past 2 years much more penicillin was used generally in Pittsburgh. Again there is the suggestion that in 1938, the year before the wide use of

sulfapyridine, the mortality rate was falling and possibly this was due to a mild infection rather than to any effects of specific treatment.

Fig. 3 shows the mortality rate in the pneumonias in our own wards at the Mercy Hospital, Pittsburgh, from 1925 to 1948 (to April 1st). There was very little change in mortality until 1937-38. We had used dextrose from 1925-30 with no change in the prognosis. The first fall in 1937-38, we lan therapy began. Since 1946 we have used only penicillin over a period of 21 months, and the low mortality rate we feel is due to this medication. With a 43% mortality in 1925, the death rate has now fallen to 11% for all cases admitted, even if they died a short time after entering the hospital, or 6% if they were treated for at least 24 hours with penicillin. No children are included, while many cases were over 60 years of age.

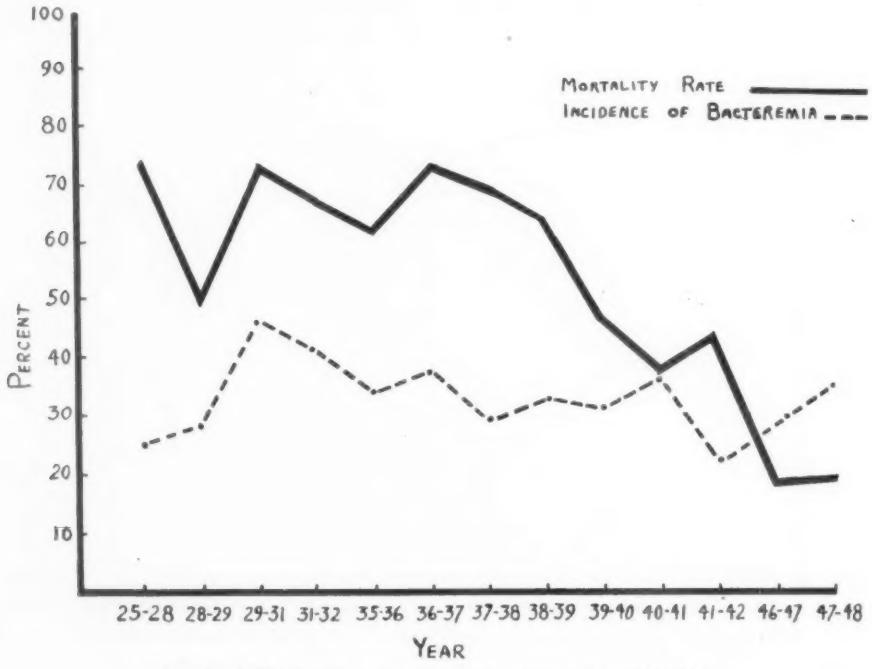

FIG. 4.—Mortality rate in pneumococcus bacteremia. 1925-1948.

believe, was associated with hydroxyethylapocupreine,[4,5] which we began to use in 1935-36, but only in adequate amounts from 1936 until 1942. Sulfapyridine was added in 1939. The fall in mortality curve, 1937-42, was therefore, due to the chemotherapy which in our wards was about equally divided between the quinine derivative, hydroxyethylapocupriene, and the different sulfonamides. The rise in 1943 and 1944 preceded a final fall after penicil-

In Fig. 4 the mortality rate of the pneumococcus bacteremia cases is shown, as is also the incidence of the bacteremia over the same period of time, 1925 to April 1st, 1948. The marked fall since 1938-39 is the main point to note as in the earlier years, up to 1937, the mortality rate was about 70%, while in the past 21 months 1946-48, the deaths were 19% with all cases counted who were admitted and 11% of bacteremia cases who had peni-

cillin for at least 24 hours. Note that the incidence of bacteremia has not varied very much and in particular with the marked fall in deaths during the past 21 months the incidence of bacteremia was actually higher, reaching 35% of cases. The fairly constant bacteremia incidence is suggestive that there has not been a great change in the virulence of the infection over this period of time. During the 3 winter months of 1948, January, February and March, we had an incidence of 40% bacteremia with Types I and II comchemotherapy. The colony counts above 100 per 1 cc. of blood are listed, and it is to be kept in mind that all were recovered cases. The large number in the penicillin column is noteworthy and in this group we would call attention to 3 of them especially, 123, 2260, and 247. This group of 3 cases was treated by mouth with penicillin.[2,7] That they recovered is proof of the value of this method of therapy. We have used this method for the first 3 months of the year 1948 in most of our cases and it is now our opinion

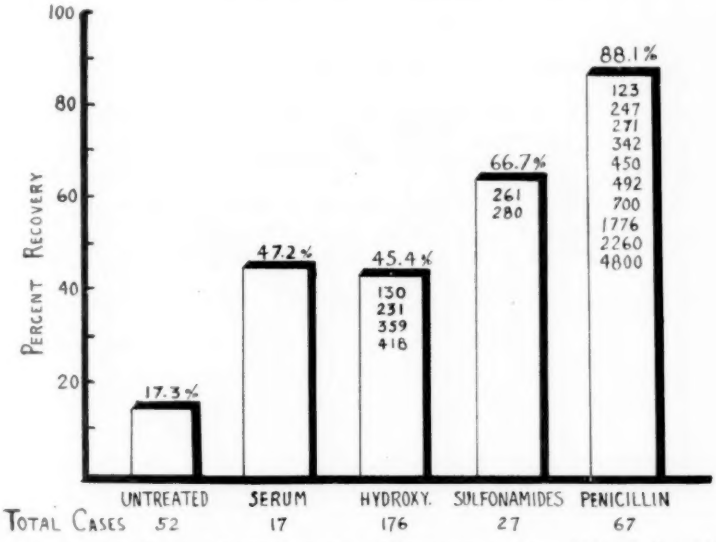

FIG. 5.—Pneumococcus bacteremia recovery rate. Colony counts above 100 listed. 1935-1948.

prising 90%. We have never seen more toxic pneumonias and yet the response to penicillin was remarkable.

Fig. 5 shows the recovery rate in bacteremia cases both non-specifically treated and specifically treated cases. Anti-pneumococcus serum, the quinine derivative hydroxyethylapocupreine, sulfonamides and penicillin were the specific measures used. The data were taken from 1935 to 1948 (to April 1st). The untreated cases were in the early years of 1935-37, as since then all cases in the hospital have had that for pneumonia the giving of penicillin by mouth is the method of choice. A comparison of oral and intramuscular penicillin in pneumonia cases is as follows: oral, 52 cases with 4 deaths (7.7%). Of these, 24 cases had bacteremia with 3 deaths (12.5%). The intramuscular injection group had 159 cases with 10 deaths (6.3%), while 43 of them had bacteremia, with 5 deaths (11.6%). The 2 methods, therefore, showed about the same results. (This work will be published in another article.) In non-specifically treated bac-

teremia cases (symptomatic therapy only) we have never seen a patient with a colony count above 15 recover. The recovered cases with colony counts below 100, which are not listed, were naturally much more frequent. The largest group of the bacteremia cases, however, were those showing pneumococci growing only in the broth culture.

Conclusions. 1. The prognosis of pneumonia in Pittsburgh for many years has almost always been grave. It has, however, very markedly improved during the last few years due to chemotherapy. In our cases of the past 21 months the prognosis has been decidedly good.

2. Penicillin is the chief reason for the good prognosis.

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THE EFFECT OF LIVER DYSFUNCTION ON THE RESPONSE TO DICUMAROL

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With the widespread use of dicumarol (3[1] Methylene bis (4-Hydroxy Coumarin)) therapeutically and prophylactically, the existence of hyperreactors was early recognized.[3] After we began to use dicumarol on the Fourth Medical Division of Bellevue Hospital, we were struck by the number of patients with unusual sensitivity to the drug who had enlargement of the liver or other evidence of liver disorder. We undertook this study to ascertain to what extent the response to a test dose of dicumarol could be correlated with certain objective and laboratory evidences of hepatic dysfunction.

Procedure. Prothrombin time determinations were made by the Shapiro modification of the method of Quick, on whole plasma, using commercial thromboplastin manufactured by the Maltine Co. of New York City. Normal prothrombin times with this material ranged from 11 to 15 seconds. By reference to a conversion table, the values obtained with each sample were expressed in terms of percent of prothrombin activity.

One hundred male subjects chosen from among the patients of 2 medical wards were tested for prothrombin activity before and following a single dose of 100 mg. of dicumarol. No patients were selected whose undiluted plasma prothrombin activity was not normal. After dosage, daily prothrombin measurements were made until the prothrombin time returned to normal, or until 4 days had elapsed with no change. In addition, most patients had cephalin flocculation tests and serum albumin-globulin determinations made in the central laboratories of the Bellevue Hospital. The results were tabulated and correlated with the clinical observations of the size of the liver below the costal margin, the presence and the amount of ascites, and the presence and degree of congestive heart failure.

Results. The results obtained in the 100 subjects are tabulated in Table I. Twenty-eight patients showed a fall in the prothrombin activity to less than 60% of normal. Of these, all but 2 had some evidence of hepatic disorder or congestive heart failure. The patients with the most profound depression of prothrombin had evidence of extensive liver damage such as ascites, positive cephalin flocculation tests, large livers or inverted albumin/globulin ratios. The lowest test of all was in a case of badly decompensated luetic heart disease.

While 93% of the 28 positive tests (below 60%) showed either congestive failure (11 cases), liver disease (12 cases) or both (3 cases), the 72 cases with tests above 60% showed only 17 (23.6%) with heart failure, 12 with liver disease (16.7%) and 3 (4.2%) with both, an overall percentage of abnormality of 44.5%.

In Fig. 1, the correlation between the positive tests and the clinical and laboratory evidence of liver disease is shown. Of 52 patients with enlarged livers (including 4 with massive ascites, rendering accurate measurement impossible) 24 (46.2%) showed positive tests. In contrast, in 48 patients in whom the liver was not palpable, there were only 4 positive tests (8.3%). Of 33 patients with congestive heart failure, 14 (42.4%) were hyper-reactors. who sometimes showed prolongation of prothrombin time for over a week, there was no correlation with the other criteria of liver function. Patients with a marked sensitivity to dicumarol in terms of prothrombin depression might be normal the next day and, conversely, a slight depression of prothrombin might take several days to return to normal.

Discussion. The exact fashion in which dicumarol interferes with the

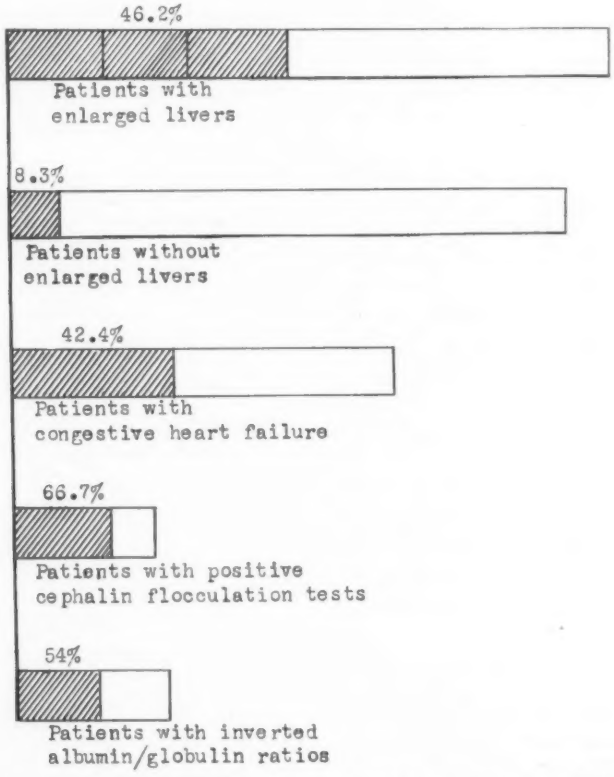

FIG. 1.—The proportion of hyper-reactors to dicumarol correlated with the size of the liver, presence of congestive heart failure, positive cephalin flocculation test, and inverted albumin/globulin ratio.

Of 12 patients with cephalin flocculation tests of 3+ or more, 8 showed prothrombin depression below 60%. Of 13 patients with inverted albumin/globulin ratios, 7 (54%) were positive.

The length of time that it took for the prothrombin time to return to normal was also studied. Aside from a few patients with advanced liver disease, elaboration of prothrombin[2] is not understood. Fatal cases of dicumarol poisoning show no specific lesions in the hepatic parenchyma. Repeated and prolonged administration of the drug leads to no permanent depression of prothrombin, which is restored to normal rapidly upon the administration of vitamin K. If vitamin K and dicumarol

are given simultaneously the effect of the dicumarol is modified or completely inhibited.[1] The chemical structure of the two substances is so similar that biochemical antagonism seems a likely explanation of their relationship. Since it has been established that prothrombin is formed in the liver,[6] and the decrease in prothrombin time accompanying states of hepatic insufficiency is well known, it is logical that dicumarol should be more effective in patients with liver disease; and a diseased liver that was still functionally adequate to meet normal demands for prothrombin might be less able to resist the action of such a toxic substance as dicumarol.

Shapiro and his co-workers[5] gave test doses of 50 mg. of dicumarol to a group of patients with liver disease and found that only in cases with a pre-existing prolongation of the prothrombin time was there any significant change. We attribute our more positive results to the larger dose of the drug employed.

Our selection of patients might be criticized on the ground that mere palpability of the liver is no evidence of dysfunction, since a low diaphragm or variation in the flare of the ribs may push a normal sized liver down, or it may become ptosed through relaxation of the ligaments that normally support it. However, we know of no easy way to distinguish between many such livers and other livers actually diseased. Certainly, the palpability of the liver is the commonest clinical denominator of liver disorder, and should incite caution in the use of dicumarol.

An outstanding finding was the high incidence of congestive failure in the positive reactors. It is difficult to believe that a liver distended to several centimeters below the ribs is not physiologically deranged, and bromsulphthalein excretion and other functional tests of the liver in congestive failure support this thesis.[4] With the increasing use of dicumarol in the treatment of coronary thrombosis and pulmonary embolism, it is important to recognize that congestive heart failure may decrease the tolerance to the drug.

Our work confirms once more the observation that the many functions of the liver may be interfered with independently of each other. We have had patients with marked evidence of liver damage who seem to have preserved well their prothrombin elaborating mechanism. We have also seen patients with alcoholic histories, large livers and no other objective evidence of liver dysfunction give strongly positive responses to 100 mg. of dicumarol. One such patient on a subsequent admission had developed a positive cephalin flocculation test. In conjunction with other liver function tests, the response to dicumarol may be of value in dating the onset and progress of liver disease.

Summary. 1. One hundred mg. of dicumarol were given to 100 patients and the effect on the prothrombin time followed.

2. Depression of prothrombin activity to less than 60% of normal occurred in 28 patients. Of these, 93% had evidence of liver disease or congestive heart failure, or both.

3. It is suggested that the response to a small test dose of dicumarol may be useful as an additional test of liver function.

The dicumarol used in this study was supplied in part by the Eli Lilly Co. The prothrombin times were performed by Mrs. Eva Roditi who also proved invaluable in many other ways.

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A CLINICAL EVALUATION OF A NEW LIVER FUNCTION TEST, THE COLLOIDAL RED TEST, IN COMPARISON WITH THE THYMOL TURBIDITY TEST*

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Ducci[2] recently reported a simplified modification of Maizels' colloidal red test[10] and claimed results fully as good as those obtained by Maclagan[8] with his modified colloidal gold reaction. Neefe *et al.* (in a footnote)[11] have substituted the colloidal red test for the colloidal gold test for the purpose of routine study in his laboratory. Accordingly, it was deemed advisable to undertake the following investigation:

1. A confirmation of Ducci's[2] and Neefe's[11] reports as to the value of the colloidal red test.

2. A comparison of the colloidal red and thymol turbidity tests on a large scale.

Methods and Material. The thymol turbidity test was performed as described by Ernst and Dotti[3] except for a slight change in the barium sulfate standard as suggested by Kunkel.[5] This change made only a slight difference in the unit readings not exceeding the experimental error in the method.

The colloidal red test was performed as described by Ducci[2]: 0.1 cc. of serum was added to 1 cc. of buffer solution, mixed, and 5 cc. of colloidal red solution was added and mixed. Results were read at the end of 24 hours. Readings were the same as those recommended by the author with the exception of his 1 plus interpretation. In this case we called the faintest precipitate visible without shaking a 1 plus reading. Each new batch of reagent was standardized by running known positive and negative sera in duplicate with old and new reagent. At present we are investigating methods of standardizing the reagent colorimetrically in order to simplify the problem of its reproducibility.

The groups of subjects chosen for this study were comparable to those reported previously[3] and consisted of the resident population of the hospital, volunteer and professional blood donors, and patients. The blood donors were all presumably at least 4 hours fasting at the time of sampling. All other blood specimens were obtained in the fasting state. All grossly lipid sera were treated separately since Kunkel[6] and Shay *et al.*[12] have mentioned the possibility of lipid sera giving false positive thymol tests.

Results and Discussion. Normal Cases. Forty-two normal cases were selected from the resident population and from this group we obtained an average thymol value of 2.5 with a mean deviation of 1.6. Four of this group showed elevated thymol values for a 9% incidence. In this same group there were 2 positive colloidal red tests for an incidence of 5%. These 2 tests were rechecked in view of the fact that the thymol turbidity value in each case was normal. These values for thymol turbidity for normals are lower than the figures reported by Ernst and Dotti.[3] This is due to the fact that they included in their series of normals a large number of blood donors which

* This study was aided in part by a grant from the Belleair Securities Corporation.

we will show give a higher thymol turbidity value than hospital personnel.

In a group of 228 blood donors the samples were divided into two groups: (1) 201 cases with clear serum and (2) 27 cases of grossly lipid serum. In group one the average thymol turbidity value was 3.4 units with a mean deviation of 2.4 units. There were 37 values above 5.0 units for an 18.5% incidence of positive tests. In this same group there were 9 positive colloidal red tests for an incidence of 4.5%. Of these 9 cases 7 also had positive thymol tests.

In separating these 2 groups now we find a lower incidence for our selected normals (9%) and a higher incidence (18.5%) for the donor group than the previously reported 13% incidence for the combined group. In re-evaluating the donor group we learned that a number of so-called "professional" donors available to our blood bank consisted of chronic alcoholics whose medical histories were unreliable. For example, one such supposedly healthy donor had a thymol value of 21.9 units, a 4 plus Hanger, and a 4 plus colloidal red reaction. The possibility exists, therefore, that a number of these people may have some form of hepatic involvement and that this factor may play a part in the high incidence of positive tests in this group, especially those in whom both tests were positive. Inability to control the fasting state in donors may also be a major factor in this group. This is borne out by the fact that a large number of lipid sera were obtained from this group alone necessitating separate treatment of these sera.

Of the 27 cases in Group 2, 17 (63%) gave positive thymols, while 3 (11%) gave positive colloidal red tests. Coincidently these 3 cases all had positive thymol tests. The average thymol value in this group was 7.4 units with a mean deviation of 5.2 units. These results would seem to confirm the observations of Kunkel[6] and Shay *et al.*[12] that lipemia interferes with the thymol turbidity test. This may also be true of the colloidal red test so that both tests should be carried out on individuals in the fasting stage only.

TABLE 1.—COMPARISON OF THYMOL TURBIDITY TEST AND COLLOIDAL RED TEST IN PRIMARY HEPATIC DISEASE

Disease	Number Of Cases	Positive Thymol Turbidity	Positive Colloidal Red
Infectious Hepatitis	5	5	5
Post Infectious Hepatitis (1 year followup)	5	3	3
Laennec's Cirrhosis	10	9	7
Hepato-splenomegaly, unknown etiology	1	0	0
Chronic Alcoholism	4	4	1
	25	21	16

Hospital Cases. In addition to diseases involving the liver primarily it is well established that many diseases can affect the liver secondarily.[1,4,6,7,9,10] Accordingly our hospital cases were divided into two groups:

(1) Patients without any known liver involvement (control group).

(2) Patients with known primary or possible secondary liver involvement.

There were 204 cases in Group 1, of which 25 (12.3%) gave positive thymol turbidity reactions. The average thymol turbidity value was 2.8 units with a mean deviation of 1.8 units. There were only 2 positive colloidal red tests in this group for an incidence of 1%. Both of these cases also had positive thymol tests and included one case of scleroderma and one case of Buerger's disease. The thymol turbidity values and the incidence of posi-

tive tests in this group are lower than those previously reported by Ernst and Dotti.[3] This may be explained by the fact that in the previous publication cases of secondary liver involvement were included in this group rather than being treated separately as in this paper.

It is apparent from the data presented that the colloidal red test has a low incidence of positive results in our control groups and in the great majority of these instances the thymol turbidity test was also positive. There were only 4 instances in which the colloidal red test was positive and the thymol reaction was normal. Two of these occurred in the blood donor group and 2 in our normal control group. The significance of this is not clear at the present time. Especially satisfactory was the low incidence (1%) in our hospital control group where the collection of fasting samples could be rigidly controlled.

We have arbitrarily divided the cases in Group 2 into those with primary liver disease and those who might have liver involvement secondary to some other disease process. Table 1 shows the results of the colloidal red test as compared with the thymol turbidity test in primary hepatic disease. Table 2 shows the results in diseases with possible secondary liver involvement. A summary of the positive individual cases is given in Table 3.

Our series of liver cases is admittedly too small to justify any conclusions at the present time. However, the limited data on liver disease does indicate several trends. It would seem that the colloidal red test correlates best with the thymol reaction in infectious diseases of the liver such as infectious hepatitis and infectious mononucleosis. In other diseases of the liver such as metastatic carcinoma, compensated cirrhosis, and chronic alcoholism, liver function tests can be unreliable and misleading.[11] The seeming lack of correlation between the two tests in this group of diseases may therefore be more apparent than real. It would also appear that, in general, there is a quantitative relationship between the thymol and colloidal red tests in that the colloidal red test becomes more positive as the thymol value increases in units. Conversely as clinical improvement becomes apparent the values for both tests decrease accordingly.

We wish to emphasize at this point that this report is in the nature of a

TABLE 2.–COMPARISON OF THYMOL TURBIDITY TEST AND COLLOIDAL RED TEST IN DISEASES WITH POSSIBLE SECONDARY LIVER INVOLVEMENT

Disease	Number Of Cases	Positive Thymol Turbidity	Positive Colloidal Red
Cardiac Decompensation with Chronic Passive Congestion of Liver	7	5	3
Polycythemia Vera with Hepato-splenomegaly	1	1	1
Metastatic Carcinoma of Liver	2	1	0
Cholecystitis and/or Cholelithiasis	12	4	3
Subacute Bacterial Endocarditis	1	1	1
Infectious Mononucleosis	9	9	9
Boeck's Sarcoid	3	3	3
Rheumatoid Arthritis	3	3	2
Rheumatic Fever	3	1	1
Sickle Cell Anemia	1	1	1
Bronchopneumonia	15	5	4
	57	34	28

preliminary one and is concerned primarily with the incidence of positive colloidal red tests in control groups. The value of any test, in part, is inversely proportional to the number of false positive tests obtained. The very low incidence of positive colloidal red tests in our control groups indicates the possible value of this test when considered from this point of view. the colloidal red test in liver disease is being carried on at present and will be the subject of a future report.

Summary. 1. A comparative study of the thymol turbidity and colloidal red tests was made and the results discussed.

2. The low incidence of positive colloidal red tests in the normal and hospital control groups as opposed to

TABLE 3.—TABULATION OF INDIVIDUAL PRIMARY AND SECONDARY LIVER DISEASES

Diagnosis	Number of Cases		Values								
Infectious Hepatitis	5	TTV*	10.3	24.0	16.5	17.9	6.8				
		CRV**	1+	5+	3+	4+	1+				
Post Infectious Hepatitis (1 year follow-up)	3	TTV	7.2	5.6	6.4						
		CRV	3+	1+	1+						
Laennec's Cirrhosis	9	TTV	7.0	6.3	19.3	5.9	8.7	6.2	15.9	7.0	14.3
		CRV	1+	1+	3+	0	0	1+	3+	3+	4+
Chronic Alcoholism	4	TTV	9.7	7.7	8.3	9.0					
		CRV	1+	0	0	0					
Chronic Passive Congestion of Liver	5	TTV	10.4	18.0	12.7	6.1	7.0				
		CRV	3+	4+	1+	0	0				
Polycythemia Vera with Hepato-splenomegaly	1	TTV	8.0								
		CRV	1+								
Metastatic Carcinoma	1	TTV	5.2								
		CRV	0								
Sickle Cell Anemia	1	TTV	9.5								
		CRV	1+								
Bronchopneumonia	5	TTV	8.9	6.2	10.0	8.7	11.9				
		CRV	0	1+	2+	2+	1+				
Cholecystitis and/or Cholelithiasis	4	TTV	10.7	8.7	5.0	5.3					
		CRV	2+	1+	1+	0					
Subacute Bacterial Endocarditis	1	TTV	5.3								
		CRV	1+								
Infectious Mononucleosis	9	TTV	8.4	10.0	11.0	14.2	6.4	10.0	6.9	18.1	10.3
		CRV	1+	2+	2+	2+	1+	1+	1+	3+	1+
Boeck's Sarcoid	3	TTV	7.4	9.3	7.9						
		CRV	2+	1+	2+						
Rheumatoid Arthritis	3	TTV	11.5	8.4	5.5						
		CRV	3+	0	1+						
Rheumatic Fever	1	TTV	5.9								
		CRV	1+								

* =Thymol Turbidity Value
**=Colloidal Red Value

Conversely, with one or two exceptions both tests correlate very well in our cases of known hepatic involvement. From our present data it would appear that the colloidal red test gives a very low incidence of false positive tests and a very high incidence of positive tests in hepatic involvement. More intensive investigation of the value of the high incidence of positive thymol reactions in these same groups together with the seemingly good correlation of these tests in infectious liver diseases would seem to justify our present opinion that the colloidal red test is a valuable liver function test.

3. In view of our findings in the donor group of controls we deem it

advisable not to use such a group as normals in studies of liver function tests.

4. Our studies confirm the work of Ernst and Dotti insofar as a high incidence of positive thymol reactions existed in all of our control groups. The lowest value obtained was 9% in a selected group of young healthy adults while our hospital group of controls gave an incidence of 12.3%.

5. The use of both tests as screening liver function tests has been valuable in our hands.

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THE TREATMENT OF SCLERODERMA

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Two recent reviews in this journal, one on the visceral manifestations of scleroderma by Beerman[3] and the other on the radiological aspects of the same disease by Pugh[34] re-emphasize the far-reaching effects on the individual of generalized scleroderma. In a disease of such eventual widespread involvement, a knowledge of the potentialities of therapy in patients suffering either from the localized type of scleroderma (morphea) or the beginnings of the generalized form is to be desired. From a study of the literature and personal experience, it appears that treatment of scleroderma of various types is far from satisfactory. This dearth of effective therapeutic means is due in part to the gaps in our knowledge of the probable pathogenesis of scleroderma, and in part to the rarity of the disease. This latter circumstance precludes the possibility of large series of well-controlled cases. Accordingly, in this discussion we shall even "grasp at a straw" by citing on occasion the results of a particular treatment regimen in one or at most a few cases.

The value of physiotherapy and climatic treatment will not be evaluated in this review beyond the statement that in the management of generalized scleroderma certain physical means such as heat, massage and hydrotherapy may be helpful in some cases. Furthermore, change in climate may yield an advantage to some patients. In fact, in his survey of the Place of Health Resort Therapy in Dermatologic Disorders, Cipollaro[10] reaffirmed the prevalent idea that "certain vascular diseases such as Raynaud's disease, pernio (chilblains), sclerodactylia and scleroderma are benefited by climatic condi-

tions. Patients with these disorders do not tolerate cold weather well. At a health resort located in a warm climate and possessing adequate facilities for medical treatment, patients with vascular diseases can be made more comfortable and their life prolonged."

It is pertinent here to call attention to previous attempts to collect the available data for the treatment of scleroderma. Among these are the massive study of Boardman[7] and the relatively recent reports of Duryee[14] on Scleroderma, Modern Concepts of Therapy (1942), and of Dennie and Morgan[12] on the Treatment of Certain Types of Scleroderma. Other sources of therapeutic suggestions and results will be specifically mentioned in appropriate places. In assessing the value of any treatment procedure in scleroderma, the factor of spontaneous improvement must always be kept in mind.

As is the case with any disease for which no one mode of therapy is specific, there are innumerable procedures which, having given good results in someone's hands, are highly recommended. A list of "recommended" treatment is given in Table 1.

TABLE I. — PROCEDURES RECOMMENDED FOR TREATMENT OF VARIOUS TYPES OF SCLERODERMA.

1. *General Supportive Measures*: Treatment of underlying causes: syphilis; neurocirculatory instability, etc.
2. *Endocrine and Ferment Therapy*: Thyroid; pituitary extract; sex hormones all types. Ferment therapy (Sellei).
3. *Vitamins*: C, D, and E (?).
4. *Miscellaneous Medicaments*: Paraaminobenzoic acid; Promin; ammonium chloride (induced acidosis); Benadryl; heavy metals (gold; bismuth).
5. *Irradiation Therapy*: Thorium X; indirect Roentgen irradiation; Radon ointment; Grenz rays.
6. *Fever Therapy*: Typhoid, hot baths.
7. *Mecholyl*.
8. *Prostigmine*.
9. *Surgical Procedures*: Sympathectomy; parathyroidectomy.

GENERAL SUPPORTIVE MEASURES: Aside from the physiotherapeutic and climatic regimens, noted above, this category of treatment includes nutritious diet and vitamins (see below), attention to underlying disease and nervous factors. The influence of syphilis and its treatment in various types of patients with scleroderma has been known for a long time. Hutchinson in 1884 reported the case of a patient with probable sclerodactylia and syphilis. Boardman[7] concluded after a thorough review of the literature that one had to admit that a large number of the cases followed infections or toxic conditions and especially syphilis. The possibility of the coincidental occurrence of the two diseases in the same patient or the presence of false positive serological reactions to the tests for syphilis must constantly be considered. On the other hand, it is not possible to dismiss summarily the occurrence of a relatively large number of abnormalities including positive Wassermann tests in the cerebrospinal fluids of patients with scleroderma. One cannot, furthermore, assume a syphilitic cause for scleroderma because it has been demonstrated repeatedly that drugs and procedures useful in the therapy of syphilis (see below) may benefit patients suffering with scleroderma.

With regard to the psychoneurogenous component in scleroderma, Stokes, Beerman and Ingraham[10] found that surprisingly little attention has been given in recent years to this aspect of the background of the vasomotor neuroses. In fact, in their review the question is raised whether the psychic factors involved in scleroderma play a primary or secondary rôle. Becker[1] on the other hand, believes that: "The syndrome embracing Raynaud's disease

and scleroderma and some other types of scleroderma appear to be on a basis of neurocirculatory instability, with alternate spasm and dilatation of the superficial blood vessels. Thyroid substance, if given in sufficient amount, vascularizes the skin, often producing improvement, although no real deficiency of the thyroid gland can be shown to exist. Our idea relative to the therapy for the conditions discussed is somewhat the same as that expressed by Christian, writing in regard to functional cardiac disease: "Endocrine disturbances, sympathetic and vagus imbalance, perverted metabolism, have been offered in the way of explanation, and treatment based on these ideas has been advised. All of these seem very fanciful, and the majority of clinicians do not accept such as playing any significant causative rôle. It seems best to regard these patients as definitely subnormal in some respect, particularly in nervous stability, largely on a congenital or developmental basis. This idea gives a good key to an understanding of the limitations of treatment."

Endocrine Therapy. In Beerman's[3] review of the visceral manifestations of scleroderma, the subject of endocrine involvement was discussed and declared to be controversial and unappraised. Similarly, the use of endocrine products in treatment remains on a relatively empiric basis. The subject has been exhaustively reviewed by Castle,[9] Boardman,[7] Seale[36] and Ehrmann and Brünauer,[16] among others. In general there seems to be an impression that thyroid extract in small doses over long periods yields benefit. When this matter is more fully investigated it appears that the reputation of thyroid therapy in scleroderma rests on a rather insecure foundation. Although there has been a relatively large number of cases of scleroderma showing thyroid involvement, clinical results have been equivocal, sometimes good and on occasion actually the reverse (Atwater). O'Leary and Nomland[29] gave thyroid gland extracts to patients in whom the basal metabolic rate was below the average. They used either thyroxine, 4 to 8 mg., or desiccated thyroid gland, 67 to 125 mg. The dosage of the drug was regulated to keep the basal metabolic rate between 0 and +10%. Although the simultaneous use of other treatment vitiated estimation of the results from the thyroid medication, they found the results from the various preparations of the thyroid gland disappointing in the group as a whole. In cases of hyperthyroidism, thyroidectomy was performed without apparent change in the scleroderma. Likewise the use of compound solution of iodin in cases of exophthalmic goitre caused improvement in the general symptoms but without effect on the scleroderma. They concluded that the value of thyroid gland extracts in the treatment of scleroderma is dependent not on the specific influence of the extract or the fact that the gland is manifesting hypofunction, but on the influence that the extracts exert on increasing the blood supply in the cutaneous vessels.

While a polyglandular deficiency has also been considered in the background of scleroderma, benefit may follow the use in a given case of a single endocrine product such as thyroid, adrenal or ovarian preparations. Oliver and Lerman[31] treated 10 patients with daily injections of 1 cc. posterior pituitary extract over a period of 15 to 30 days, followed by a rest period of one month. Control patients were given 1 cc. of pancreatic extract with negative results. The immediate effect of the posterior pituitary extract was marked pallor, lasting 10 to 15 minutes followed by a flushing of the skin of longer duration. All the patients complained of abdominal cramps associated with bowel movements. All 10 patients sustained improvement, permanent in some of them. The increase in erythema in or about the lesions in 3 cases of morphea indicated an increase

in the blood supply. This increased blood supply, rather than a substitute true endocrine replacement effect, may be the factor responsible for the improvement. Contrary to Oliver and Lerman's experience, O'Leary and Waisman[30] found that daily injections of posterior pituitary over a long period were of slight benefit in their patients with acroslerosis.

Although Duryee[14] included the female sex hormones among the preferred methods of treatment the relatively scanty literature is far from enthusiastic. The similarities of generalized scleroderma and dermatomyositis (Dowling and Griffiths[13]) suggest that the recent work of Lamb, Lain, Keatty and Hellbaum[24] on steroid hormones might be extended to the problem of the therapy of scleroderma. These authors observed significant clinical improvement in 4 cases of dermatomyositis by the injection of testosterone proprionate. Clinical improvement was accompanied with significantly increased ability to retain exogenous creatine, increased muscular strength and moderation of cutaneous lesions. Best results were obtained in the earlier cases before permanent vascular and muscular changes had occurred.

Sellei,[37] while championing the duality of scleroderma and acrosclerosis, has included scleroderma among the group of diseases he has called "dysfermentoses". This term is used to designate those diseases arising in various tissues as a result of abnormal enzyme action, such as by ferments produced in the skin, bone marrow, and nervous system. He advocated a so-called ferment therapy for them. Administration of fresh or dried pancreas, as well as other digestive ferments, has yielded improvement with actual softening and disappearance of the cutaneous induration. Again, best results are obtained in the earlier phases of the process before atrophy has taken place. It is also of little use in acrosclerosis. According to this investigator, ferment therapy is based on a "chemical system" composed of enzymes, ascorbic acid and metallic catalysts. For best results it is necessary to have the enzymes and other preparations fresh, given continuously and for a long time. The ferments must be given about 1½ hours before meals. Sellei prescribed 150 to 200 gm. of raw pancreas (mixed with mayonnaise, or leafy green vegetables containing ascorbic acid or sweet peppers, tomatoes, cucumbers, or an anchovy spread, or mushrooms). The remaining meals are left to the choice of the patient. However, with every repast there must be taken 3 pancreatin tablets, ascorbic acid, and iron. After several weeks the raw pancreas is replaced by pancreatin tablets and still later by raw liver (200 to 300 gm. daily) prepared as was described for the pancreas.

Sellei's work has not received widespread confirmation. Urbach[43] has found it of interest and Becker and Obermayer[2] noted that the administration of raw pancreas was of value in 2 patients with generalized superficial scleroderma. However, O'Leary and Waisman[30] have not seen any impressive effects from the use of insulin-free extracts of pancreas or of other tissue extracts.

VITAMINS. A growing literature on scleroderma involves the use of vitamins in treatment. The data regarding vitamin D are convincing. Those involving the use of vitamin C and those indicating the possible value of vitamin E are highly conjectural.

Disturbance of calcium metabolism is consistently found in scleroderma. This is especially prominent when scleroderma occurs together with calcinosis, such as is the case in the so-called Thibierge-Weissenbach syndrome. Since there is evidence that scleroderma may in some way be related to hyperfunction of the parathyroid gland, and since the latter has a definite relationship to calcium metabolism, it is obvious that

this may be the basis for the disturbed calcium metabolism in this disease. Cornbleet and Struck[11] found that both calcium and phosphorus are retained in the body. This retention can be accounted for, for the most part, by the abnormally small quantities excreted in the urine. Large doses of viosterol markedly increase the calcium content of the urine and thereby produce a loss of calcium and phosphorus from the body. Cornbleet and Struck[11] offer an hypothesis to the effect that scleroderma is initially due to a toxin which injures the collagen syncytium and that the injured tissues secondarily take up calcium. This disposition of calcium may account for the frequently observed positive balance in scleroderma. As a result of this reasoning Cornbleet and Struck tried, with success, 200,000 to 300,000 international units of vitamin D daily in 11 cases of scleroderma. In 1939 Hummel[22] noted that AT-10 (dihydrotachysterol) was of use in scleroderma. At least 4 months of continuous treatment is required for improvement; and scerodactylia responds more slowly than generalized scleroderma. Similarly Bernstein and Goldberger[5] found 1 cc. daily doses of dihydrotachysterol for 2 to 4 week periods until 75 cc. had been administered, of benefit in a 70 year old woman with scleroderma. There were no changes in the blood calcium or phosphorus values during treatment. Norman[27] also studied the effects of 50 to 100 thousand units a day of vitamin D on 3 women with scleroderma all of whom had Raynaud-like changes in the hands and feet. All sustained pronounced general improvement with restoration of the skin practically to normal and an increased joint mobility. There was depression of the ovarian function in all 3 patients, and relapse occurred after treatment was stopped. Duryee[14] felt that although his experience with dihydrotachysterol has not produced demonstrable improvement, it seemed to have some beneficial effect on one case in which parathyroidectomy had been performed. Since dihydrotachysterol is a sterol, its effect on calcium metabolism may be similar to that of estrogens. He felt that further investigation of this product is warranted.

Although there is apparently no evidence for vitamin deficiency in scleroderma but because vitamin C has potentialities in promoting wound healing, Duryee makes vitamin C a part of his routine of therapy. Indications that vitamin E may have some merit in scleroderma are found in the influence of this preparation on vascular disease (Shute, Vogelsang, Skelton and Shute[39]). The recent report of Burgess and Pritchard[8] on the successful treatment of ulcers of the legs with vitamin E, and their use of it in lupus erythematosus seems to support the ability of the tocopherols to regenerate collagenous tissue.

Para-aminobenzoic Acid. In a preliminary statement, Zarafonetis[47] reported on the use of paraminobenzoic acid preparations in unspecified dosage in 5 patients with a wide range of scleroderma tous involvement. There was improvement in 4. It appears to be best in the most extensive cases. There is a gradual softening of the affected parts with an increased range of motion. This agent deserves further critical study because of its potential toxicity.

Promin. In a preliminary report Wuerthele[45] stated that she had reason to suspect a bacterial origin for scleroderma. On the supposition that this organism was a mycobacterium as in leprosy and tuberculosis, she treated a patient with scleroderma with promin in tragacanth jelly (sodium P,P^{1}-diamino - diphenyl sulfone - N - N^{1} didextrose sulfonate). The patient was able to return to work in 2 months. In a later paper[46] Wuerthele-Caspe and her coworkers reported the finding of an acid-fast bacillus in 5 cases of scleroderma (in sputum, blood, nasal and

subcutaneous tissue and has been grown from blood). All the patients treated with the promin locally, orally or by injection, showed definite, responsive changes. This work needs confirmation.

Ammonium Chloride in the Treatment of Scleroderma. In spite of Leriche and Jung's[25] feeling in favor of the operative (parathyroidectomy or sympathectomy) treatment of scleroderma, they did not venture to propose surgical treatment at the onset of 2 cases of scleroderma, and their patients passed through the gamut of medical treatment. In the 2 years preceding the date of publication they tried ammonium chloride which increases the elimination of calcium by way of the urine. They cite in detail a case of a woman with early scleroderma in plaques on the face which had resisted various medicaments and which continued to spread. Blood calcium was .103 gm. (hypercalcemia). She was placed on the following regimen designed to increase the elimination of calcium which Pautrier and his collaborators had shown was increased in scleroderma. 1, Acidifying regimen: Take bread, pastry, rice, sweetmeats, meat and fats. Avoid milk, green vegetables and fruits. 2, Ammonium chloride 3 gm. daily. After 20 days of this regimen there was a marked improvement in the skin and the blood calcium fell to 0.089. The patient lapsed treatment and while under thyroid extract at another physician's hands there was a relapse of the local and systemic complaints. Resumption of the ammonium chloride was followed by rapid improvement. Since that time on numerous occasions the symptoms recurred when the treatment was stopped. New lesions appeared even when thyroid-parathyroid extract was used. This makes the good effects of the ammonium chloride appear to be more than a coincidence. The same results were obtained with a second case of scleroderma (of the extremities). We have personally seen similar results in several of our patients. The mode of action of the ammonium chloride is not definitely known. An acidifying regimen can double the urinary elimination of calcium. By the same mechanism, the acidosis produced by the large doses of ammonium chloride may considerably increase the excretion of calcium, may modify the pH and may produce an increase in the ionization of the calcium.

Benadryl. O'Leary and Farber[28] have administered beta-dimethylaminoethyl benzhydryl ether hydrochloride (benadryl) to 9 patients who had acrosclerosis and to 4 who had scleroderma. The benadryl was given by mouth in amounts varying from 200 to 800 mg. a day. A chief complaint of the acrosclerotic patients was their inability to flex their fingers or to make a fist. During the first 2 weeks of therapy 7 of the 9 patients who had acrosclerosis were able, because of the rapid disappearance of edema from their hands, to bend their fingers and to make a fist, and there was a decrease in the cutaneous edema of 2 of the 4 patients who had scleroderma. Sustained benefit, however, was achieved for only 2 of the 9 patients who had acrosclerosis. Pyribenzamine and other antihistaminics may also yield similar results.

Heavy Metal Therapy. Although the coincidence of syphilis and scleroderma improved by anti-syphilitic therapy has been noted above, heavy metals (gold and bismuth) have exerted a non-specific beneficial effect in various types of scleroderma. Preininger,[33] for example, believing scleroderma to be an infectious process, used gold in the treatment of 3 cases of the diffuse type, 2 of the circumscribed variety, 2 of acrosclerosis and 1 of scleroderma. Treatment consisted of intramuscular injections of 0.01 to 0.05 and 0.1 gm. solganal B in children and 0.25 to 0.5 gm. in adults. The patients also received bismuth injections in conjunction with the gold. The treatment produced marked clinical improvement in

all patients except those with acrosclerosis. In the case of localized scleroderma, Flood and Stokes[18] taking the lead from 2 French reports[34,38] dealing with the successful treatment of this form of scleroderma with bismuth compounds, obtained excellent results in 2, good in 4 and fair in 1 case. Bismuth hydroxide ("Muthanol") and solution of sodium bismuth iodide and sodium iodide in propylene glycol containing saliginin and acetic acid (Iodobismitol) were used, but they noted that bismuth subsalicylate is also effective according to other reports. Recent use of oral bismuth preparations suggests the possibility of their wider application to the therapeutic regimen of scleroderma (Stryker *et al.*[42]).

Irradiation Methods of Therapy. The use of thorium-X ointment in scleroderma was first recommended by Bloch.[6] In 1933 Epstein[17] obtained good results in all the patients he treated with this means, but best results were obtained in the circumscribed form of the disease. He employed an ointment of 1000 to 2000 electrostatic units in 1 gm. The ointment is applied on a wooden applicator to the affected areas, covered with gutta percha, bandaged and left in place for 18 to 48 hours, usually 24 hours. Treatments are given at 6 to 12 week intervals and as many as 10 treatments have on occasion been given to one area. No late sequelae had been observed after 15 years of trial in the Breslau Clinic.

Indirect roentgen irradiation therapy of the central and vegetative nervous system was found to be of some value in stopping the unfavorable progress of scleroderma by Foerster[19] and by Halter and Lundt.[20]

Strassburger[41] has suggested the use of Radon ointment for scleroderma. Grenz rays have also been used with benefit in a limited number of cases.[23]

Fever Therapy. Fever treatment with intravenous typhoid vaccine injected weekly for 10 to 20 weeks has been tried with some success in acrosclerosis and diffuse scleroderma. Recently Dennie and Morgan[12] described the fever treatment of circumscribed scleroderma by means of hot water baths. In 1934 one of these investigators treated a case of central nervous system syphilis with hot water baths. This patient also had a large plaque of morphea on the back. Follow-up examinations revealed a startling regression of the sclerodermatous lesion and after a period of 6 months the sclerotic process had completely disappeared. There was only residual pigmentation where a purplish halo ¼ of an inch wide had surrounded the original lesion with mild atrophy over the site of the plaque. This result encouraged the writers to regard hot baths as a promising therapeutic measure in scleroderma, since they felt that the vascular dilatation and resultant improved circulation must have been the main factor in overcoming the basic angiotrophoneurosis. However, it was also felt that through this medium of raising the body temperature, the reticulo-endothelial system would stimulate the body's natural defense mechanism. Thus if any toxic factors were present as etiological agents, the chances of their suppression should be enhanced.

Since this original experience, Dennie and Morgan have tried hot baths on several cases of scleroderma, including the generalized or diffuse types, as well as with acrosclerosis. Real success has been confined to circumscribed scleroderma of the plaque and linear types and morphea guttata. Up to the present they have had complete regression of these types of lesions in 3 cases over a 12 year period. In only 1 of these 3 cases, however, were hot baths the only attempted therapeutic measure. Glandular extracts from the ovary, thyroid, pituitary and pancreas and a concentrated vitamin A and D preparation were tried first but little or no success was noted until fever therapy by means of hot baths was instituted.

Dennie and Morgan's method of administering hot water baths can be utilized by the patient at his home, and thus is inexpensive and can be easily carried out. The only equipment necessary is a bath water thermometer, which can generally be purchased from any large dairy, a clinical thermometer, a bathtub with hot, running water, two cotton and two woolen blankets, bath towel and ice cap. An additional member of the family must render assistance at home for this method of therapy.

Mecholyl Iontophoresis. In 1937 Duryee and Wright[15] reported on their experience with methyl choline iontophoresis. Up to 1942 they had used it for 9 years and at least 50 patients had received this form of treatment. There was marked or moderate improvement in 60% of these cases. It is not a specific treatment but causes increased vascularity of the involved parts. Rittenbruch[35] found acetylcholin to act definitely on the mobility of the joints as well as on the skin diseases. O'Leary and Waisman[30] observed no outstanding results from the oral or hypodermic use of mecholyl chloride (acetyl beta methyl choline chloride) in acrosclerosis.

Prostigmine. Based upon Perlow's[32] use of prostigmine in the treatment of peripheral circulatory disturbances, O'Leary and Waisman[30] found the oral use of the bromide or the methyl sulfate subcutaneously of some value in the treatment of their patients with acrosclerosis.

Surgical Therapy of Scleroderma. Since Leriche proposed the treatment of scleroderma surgically by an interruption of the function of the sympathetic nervous system, a large group of investigators have treated a varying number of patients by this method with good or indifferent results. The literature on this surgical approach to the problem of scleroderma has been carefully collected by Hämäläinen and Söderlund,[21] to which paper the reader is referred. All agree that there is immediate improvement of variable degree but the final results leave much to be desired. Duryee[14] has summarized his views against sympathectomy as follows: "1, In those cases referred to our clinic in which this procedure has been carried out, no permanent improvement was noted. 2, The nature of the cutaneous lesions would prevent an increase in the vascular supply in the involved area even if the element of spasm were removed (Printzmetal). 3, The spasm which is present may occur independently of the nerve supply (Lewis). 4, In the majority of the patients the affected vessels are generalized (*not confined to those affected by the sympathectomy.* Eds.). 5, The improvement in vasodilatation is usually temporary (Johnson and Berheim and Garlock)."

Parathyroidectomy[4,26] merely influences one factor, the calcium metabolism in scleroderma. Some investigators have reported good early and late results and others have found this procedure wanting.

On the whole, in view of the indifferent results from surgery at the hands of conservative authorities, surgical methods should be the last resort in scleroderma of all types.

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OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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THE OVERMEDICATED NASAL CAVITY

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NASAL vasoconstrictors are among the most important drugs available to rhinologists. The weight of evidence indicates that these drugs afford symptomatic relief only and are not curative. Nasal vasoconstrictors can relieve nasal congestion for varying periods of time and when judiciously employed aid in promoting adequate drainage from the paranasal sinuses. Even temporary relief from the discomfiture of nasal obstruction is a boon to the individual so afflicted, and a number of sympathomimetic amines have come to assume a legitimate place in the therapeutic armamentarium.

Animal experimentation as a basis for observing the histophysiologic effect on nasal mucous membrane of various nasal preparations is well recognized, but not always practiced. Although it is obviously advisable to determine the histophysiologic effect of drugs on the normal nasal mucous membranes of experimental animals before advocating their widespread use in human beings, knowledge of undesirable caustic reactions sometimes comes initially via the patient's nasal cavity.[4a] If the truth be stated bluntly, this is literally paying through the nose. Years after its position in rhinology had been liquidated by clinical trial-and-error, it was learned, for example, that when mercurochrome is introduced into the nasal cavities of experimental animals, the substance will pass through the mucous membranes of the nasal cavity and paranasal sinuses, through the turbinates, through the bony walls of the frontal sinus, and even through the dura, to discolor the cortex of the brain in much less than 2 hours![9]

Experiences of the past decade have demonstrated that it is possible to curtail greatly, if not completely, two man-induced sequelae to promiscuous nasal medication — lipoid pneumonia and argyrosis. Recognition of the shortcomings of mineral oil as a vehicle for nasal medicaments, and its subsequent omission in numerous preparations, in all probability have diminished the incidence of lipoid pneumonia from this source. On the other hand, if one were to propose an aphorism to describe the overmedicated cavity, it would run something like this: over-treatment can sometimes prove just as damaging as the absence of treatment. It is known, for instance, that argyrosis of the nasal mucous membranes can be due to prolonged administration of silver salts in direct contact with the nasal mucous membranes. Bryant[1] found silver deposits in the biopsy specimens of nasal tissues of rabbits after having instilled various silver salt preparations intranasally for a period of 8 weeks. He maintains that the promiscuous use of silver-containing nasal medicaments is dangerous and accomplishes nothing that cannot be accomplished safely and more efficiently by other means.

According to Kully,[8] the action of sympathomimetic amines is chiefly on the blood vessels, although the secretory function is also involved. The subepithelial capillaries, the arterioles and the venous sinuses of erectile tissues are subject to constriction, and nasal secretion is diminished. If vasoconstriction is severe or prolonged, a secondary vasodilatation ensues, involving the deeper venous sinuses more than the subepithelial vasculature and leaving the mucous membranes blanched. Occasionally, the secondary reaction may be more evident and prolonged than the primary constriction. Secondary vasodilatation is influenced chiefly by the type and amount of the drug used and by sensitivity of the vasomotor mechanism.

In individuals in whom sensitivity to nasal vasoconstrictors has been established, Wright[18] declares that the predominant complaint is nasal stuffiness. The patient who overmedicates his nasal cavity usually does so to relieve a sensation of congestion. Usually the underlying condition is an acute cold or a recurrent attack of chronic sinusitis. The use of nose drops may have been initiated on the patient's own responsibility or in some instances on the advice of physicians. As the practice of frequent intranasal medication continues over prolonged periods of time, the relief becomes less pronounced; finally, little or no relief is obtained. Clinically, the mucous membranes of the overmedicated nasal cavity are often indistinguishable from tissues seen during acute allergic episodes. In Wright's[18] experience all the patients with nasal sensitivity to a nasal vasoconstrictor have employed synthetic preparations and not natural ephedrine products. In general, many synthetic products provide a greater degree of vasoconstriction and a more prolonged effect than ephedrine.

Excessive use of sympathomimetic amines for a prolonged period of time can cause a clinical syndrome appropriately termed "vasomotor rhinitis medicamentosa." Fortunately, nasal sensitivity to vasoconstrictors can be checked rapidly by discontinuing the offending medicament. Vasomotor rhinitis medicamentosa, like lipoid pneumonia and argyrosis, is man-induced; its saving grace is the promptness with which cures can be established. No rational employment of nasal medication will countenance deliberate and promiscuous overindulgence.

Ryan[12] undertook a study to observe the histologic changes in the nasal mucous membranes of rabbits produced by the overuse of 2 types of nose drops. The first preparation was a 0.125% solution of dl-desoxyphedrine hydrochloride in a stabilized aqueous vehicle, 1.25% of anhydrous sulfathiazole sodium and 1.25% of sulfadiazine sodium; the second preparation was a solution of naphazoline hydrochloride (privine hydrochloride). Each of these preparations destroyed the cilia and the epithelium was transformed into stratified squamous epithelium. The subepithelial layer underwent fibrosis. The blood vessels became dilated and remained dilated for several weeks. Constriction and sclerosis of the blood vessels was observed at a later date.

The effects of prolonged medication with nose drops, nasal sprays and nasal inhalers of vasoconstrictor amines were studied in normal adult rabbits by Butler and Ivy.[2] The studies revealed that volatile inhalers and nasal sprays are similar in intensity and duration of effects produced, while nose drops appear less effective as a method of medication. The effects on the nasal mucous membrane produced by repeated administration of inhalers and sprays are similar, and both produced less pathologic change than that resulting from the use of nose drops. It seemed to the investigators that the selection of methods of medication in acute rhinologic conditions should be limited to

nasal inhalers and sprays in most instances. When it is desirable to direct medication to a specific area in the nasal chamber, such as the ostium of a paranasal sinus, nose drops may be the method of choice. In conditions requiring prolonged and repeated medication, sprays or inhalers are proposed methods of choice. In commenting on this investigation, it may be pointed out that clinical deductions were made from histologic study of the mucous membranes overlying the nasal septum. In actual practice, the purpose of liquid nasal medication as well as other means of intranasal medication is to shrink the mucous membranes of the turbinates in order to obtain relief rather than to constrict the mucous membranes overlying the nasal septum.

Various authors have called attention to the secondary congestion arising from use or misuse of privine hydrochloride. In general, the collective experiences appear to have been closely parallel. Feinberg and Friedlaender[5] comment on more than 75 individuals in whom symptoms of nasal congestion were aggravated or prolonged by the continued use of the vasoconstrictor; Schiller[14] describes the secondary congestion arising from the drug in seasonal hay fever; Gollom[6] writes about persistent nasal congestion following the use of the medicament; Mertins[10] discusses 3 cases of rhinitis medicamentosa from excessive self medication; and Putnam and Herwick[11] report a case of naphazoline hydrochloride dependence of 23 months duration. Talmage[17] describes the case of a 62 year old woman complaining of continuous nasal blockage. The patient had been using an 0.1% solution of privine hydrochloride for more than a year, employing more than 1 ounce of the medicament each week. Her dependence on the drug subsided completely within 3 weeks after its discontinuance.

House and Carey[7] call attention to the fact that children may exhibit a different response to ephedrine and privine hydrochloride than that of adults, with sedation following a period of ½ to 1½ hours of mild stimulation. The systemic effects that may follow administration of the latter drug to children include prolonged hypertension with peripheral vasoconstriction; mild cortical stimulation, followed by depression; depression of the basal centers; and an ability to resemble and potentiate the action of the barbitals in depression of respiration. In this connection, Childrey and Essex[3] point out that absorption from the mucous membranes of the nasal cavity and paranasal sinuses is much more rapid when these membranes are inflamed. This may offer one explanation for an occasional case of systemic reactions. There is, in addition, also the possibility of sensitivity or idiosyncrasy to nasal medicaments.

That ephedrine and other types of nasal vasoconstrictors can cause secondary congestion is alluded to by Scarano[13] who observed the secondary reactions (returgescence, atony and bogginess) following frequent daily intranasal instillations of ephedrine and amphetamine in oil. Varying degrees of secondary reactions were noted in 5 of 25 individuals utilizing ephedrine, while reactions from amphetamine were virtually negligible. During a period of 6 years Sternberg[16] followed 32 patients whose nasal discharge and obstruction were due more to the continuous use of vasoconstrictors than to the underlying allergic condition. Eleven vasoconstrictors were employed and he observed no evidence as to which one produced more damage.

Seydell and McKnight[15] write about 8 individuals with distressing disturbances to the olfactory sense which, they are convinced, are attributable to the intranasal instillation of 2 different preparations of tyrothricin, both, however, containing tyrothricin in concentrations of approximately 1:5000. The

solutions were applied by spray and as nose drops. Anosmia or parosmia developed after a solution of tyrothricin was used in the nasal cavity. These symptoms have been persistent, ranging in duration from 4 to 8 months. The symptoms have outlasted by months the condition for which the solutions were originally prescribed. At the time of the report none of the patients had regained a normal sense of smell. Most of the patients thought there had been some improvement, at least as far as intensity of parosmia was concerned.

The problem of producing new sympathomimetic amines is of great importance and deserves more attention in the pharmaceutical world. Until pharmacologists happen upon an abuse-proof type of liquid nasal medicament, in Fabricant's[4b] opinion, improved medicine droppers, among other measures, are urgently required to assist patients in clinical utilization of controlled amounts of nose drops. The case for controlled dosage could be assured by the manufacture of a medicine dropper that would permit automatically a desirable number of nose drops to be released when instilling liquid nasal medication. A truly effective medicine dropper would go a long way toward abolishing some of the tendency toward uncontrolled overdosage and would assist materially in eradicating the fear of producing unpleasant side-reactions through overdosage. Perhaps the need for an ideal sympathomimetic amine will be answered at some future date—but until then specific measures for overcoming the abuse and misuse of liquid nasal medication through overdosage are required.

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PROCEEDINGS OF
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Neuronal Changes Associated With Tetany of Alkalosis and Hypocalcemia. HAROLD KOENIG, M.D., M.S., PH.D., and RUTH KOENIG, M.B. (Dept. of Anatomy, School of Medicine, Univ. of Penna.). These studies were carried out to test the hypothesis that the basophilic component of Nissl substance in the cytoplasm of neurons serves as a source of energy for neural activity and may be depleted if this activity is sufficiently great and prolonged.

Tetany greatly augments neural activity by producing repetitive spontaneous discharges both in motor and in sensory neurons, and probably also in interneurons. Hypocalcemic tetany was produced by intravenous administration of sodium citrate solution in one cat, and of a solution of mono-and dibasic sodium phosphate at pH 7.4 in another cat. Alkalotic tetany was produced by intravenous administration of a solution of sodium bicarbonate in 2 cats. Blood pH rose from 7.4 to 7.8 - 7.9. All 4 animals were kept in a severely tetanic state for 2 hours and then fixed by perfusion of the vascular system along with 2 normal control cats.[1] The brain and cervical enlargement of the spinal cord were stained with thionin[2].

The large motor neurons of the spinal cord and brain stem were studied. In hypocalcemic tetany, these cells for the most part stained more lightly. The Nissl bodies were less sharp, lighter and fragmented as compared with the control sections. In alkalotic tetany, these cells were distinctly darker than comparable cells in control sections. The Nissl bodies were less sharp, but darker and often larger, and the cytoplasmic background showed a greatly increased basophilia.

The results obtained in hypocalcemic tetany are consistent with the energy theory of the function of Nissl substance. Alkalotic tetany, however, resulted in an increase of cytoplasmic basophilia. It is suggested that anoxia resulting from cerebral vasospasm produced by alkalosis, or the effect of the pH shift on intracellular enzymes involved in Nissl body metabolism, or both, are responsible for these changes.

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Effects of Ablation of Cerebellar Cortical Tactile Areas in the Cat. W. W. CHAMBERS, PH.D., and C. N. LIU. (Dept. of Anatomy, School of Medicine, Univ. of Penna.). Ablations of discrete portions of the anterior lobe of the cerebellum which are situated laterally to the vermal veins and coincide with the tactile receiving areas[1] have been performed. These areas are the tactile areas for the fore and hind foot.

Destruction of the fore and hind foot areas resulted in an ipsilateral loss of tactile placing reactions, overstepping of the ipsilateral limbs and reductions of hopping reactions. These symptoms have persisted for as long as 8 months.

Similar symptoms follow destructions of either the fore foot or hind foot tactile area but involve only the limb which corresponds to foot area removed (*i.e.*, ablation of fore foot tactile area results in symptoms limited to the ipsilateral fore leg.)

That these changes in the postural reflexes, especially the enduring loss of the tactile placing reactions, may be due to increased postural tone is

unlikely, for the increase in postural tone in the affected limbs was minor as compared to the increased tone associated with medial vermal and, or, fastigial nuclear lesions, which are unaccompanied by loss of tactile placing reactions. Further evidence for the discrete symptomatology of the tactile area of the anterior lobe was obtained by ablations of nearly all parts of the medial vermis and cerebellar hemispheres without any impairment of placing reactions.

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The Functional Significance of some Thalamo-cortical Mechanisms. Herbert H. Jasper, M.D. (Montreal Neurological Inst., McGill Univ.) (By invitation.) The results of 2 types of experiment on the thalamus are recorded: 1, analysis of various local thalamic structures by stimulation of not more than 1 c. mm. of carefully located areas in the thalamus using the Clark stereotaxic instrument and recording the activity from over the cerebral cortex; 2, implantation of stimulating electrodes in different parts of the thalamus and observing subsequently the changes in behavior as recorded by cinematography following stimulation of various portions of the thalamus in the unanesthetized freely moving animal.

The results of the first series of experiments reveal 2 types of thalamo-cortical organization: *a*, the local nuclear cortical system, which involves a point to point projection from the relay nuclei to the sensory areas of the cortex and from the association nuclei such as the pulvinar and the dorso-medial nucleus to other cortical areas. This local point to point projection seems to be just as precise for the dorso-medial nucleus, for example, to various portions of the frontal lobe, as is the localization of ventralis posterolateralis to the postcentral gyrus. Overlapping this local system, there is, *b*, a diffusely projecting system, which we have called the *thalamic reticular system* which includes the intralaminar fibres and nuclei and the reticular nucleus. In the central core of this reticular system, which in the cat occupies the rostral portion of the massa intermedia, it is possible to stimulate over an area of not more than 2 to 3 sq. mm. in size and obtain control of spontaneous rhythmic activity of the entire cortex. This control is maintained even after destruction of the thalamic nucleus which projects in a local manner to this same cortical area so that it is an overlapping though diffuse projection system with particular functions, we believe, in the general regulation of excitability and possibly timing of events in various areas of the cortex relative to each other. From a portion of this system, it was possible to obtain the bilaterally synchronous wave and spike discharge very comparable to that seen in petit mal epilepsy.

The stimulation of this system in the unanesthetized animal with implanted electrodes reproduced a form of seizure, during a period after the end of stimulation, which simulated as closely as could be expected the petit mal lapse of responsiveness, without convulsive movements. With higher frequency and higher intensity stimulation of the same area, generalized major convulsive seizures were produced.

It was postulated that this thalamic reticular system which has its overlapping diffuse but yet topographically organized projection to all cortical regions must have some general facilitory and possibly also inhibitory effect on cortical activity, perhaps homologous with the functions recently described by Magoun and Rhines for the bulbar reticular system.

BOOK REVIEWS AND NOTICES

ADVANCES IN MILITARY MEDICINE. Edited by E. C. ANDRUS, D. W. BRONK, G. A. CARDEN, JR., C. S. KEEFER, J. S. LOCKWOOD, J. T. WEARN, M. C. WINTERNITZ. Assoc. Editor, TUCKERMAN DAY. Foreword by A. N. RICHARDS. 2 volumes. Pp. 965; 94 ills. Boston: Little, Brown, 1948. Price, $12.50.

THE Office of Scientific Research and Development (OSRD) was Democracy's way to mobilize and correlate the nation's scientific resources in brains and equipment to meet the threat of totalitarianism during World War II. This 2-volume work deals with the activities of one of the subdivisions of OSRD: The Committee for Medical Research. By pooling their available basic information on topics germane to military needs and by assigning themselves the several angles of experiments to convert that information into practical uses, the medical scientists (nearly 1700 doctors and 3800 other trained investigators) were able to bring the methods of mass production and the assembly line to bear on the problems of military medicine and so to achieve, in a short time, results that might have been delayed for decades. (It must be pointed out that *first steps*, or the discovery of basic information, are overwhelmingly the work of the individual scientific "prospector", and are not amenable to mass-production methods.)

The material of these volumes is grouped according to the 6 subdivisions of the Committee: medicine, surgery, physiology, chemistry, aviation medicine, and malaria, with additional sections on penicillin and on sensory devices to aid the blinded. The 54 chapters are written each by a recognized authority on and participant in the particular phase of investigation, and represent the essential facts as set forth in about 1300 publications (whose references are an appendix of the work). The importance and manifold interest of the volumes are attested by such chapter headings as The prevention of infection in accidental wounds; The application of penicillin to surgical problems; New surgical plastics and hemostatics; The study of crash injuries and prevention of aircraft accidents; Motion sickness; The history of plasma fractionation: blood substitutes; Methods of preservation of whole blood; The development of new insecticides; New insect repellants; New rodenticides; The clinical testing of antimalarial drugs; Research in the development of penicillin. The manner of presentation is in simple terms so that non-medical scientists will find it easy reading.

This publication is not merely the history of advances in military medicine: it is a record of brilliant achievement for all phases of medical practice. Every physician should read it with profit as well as interest and pride in his profession. R. K.

HOSPITAL TRENDS AND DEVELOPMENTS, 1940-1946. Edited by A. C. BACHMEYER, M.D., Univ. of Chicago, and GERHARD HARTMAN, Ph.D., Univ. of Iowa. Pp. 819; New York: Commonwealth Fund, 1948. Price, $5.50.

THE material used in this new book has been carefully selected from countless articles written during this period on the numerous phases of activities connected directly or indirectly with the development of the modern hospital. The editors, who are well known in the field of hospital administration and teaching, have gathered these articles into one volume in order that people interested in the hospital field may have access to recent writings by qualified people on the various subjects without undue reading of all the literature that has been published.

This is a companion to their earlier volume, THE HOSPITAL IN MODERN SOCIETY, which was published in 1940. R. B.

ORAL AND DENTAL DISEASES. By HUBERT H. STONES, M.D., Prof. of Dental Surgery, Univ. of Liverpool. Pp. 896; 926 ills., many in color. Balt.: Williams & Wilkins, 1948. Price, $18.00.

THIS is an excellent book. While designed particularly to meet the needs of dental students in the subjects of Oral Pathology and Oral Surgery it may also be recommended as a reference book for practitioners of medicine and dentistry. Oral lesions which are manifestations of systemic origin as well as those of local origin are considered in detail. Clinical features are fully described and illustrated with excellent photographs, many of which are in color. There are short but precise sections on treatment. Emphasis, however, is laid on etiology and histopathology and the many photomicrographs are well chosen and add considerably to the usefulness of the text. Recent research is cited frequently and its bearing on disease in the mouth competently discussed. The book gives evidence of the author's great experience in teaching and in examining students in various universities as

well as personal experience in investigative work.

It is difficult to select outstanding chapters for comment. Those on endocrine disturbances and nutritional deficiencies discuss experimental work and its relation to clinical diseases and malocclusion of the jaws and teeth are well treated. There are four chapters on stomatitis and allied diseases of the oral mucosa. The chapter on tumors is comprehensive and well illustrated. There is no mention, however, of fibrous dysplasia of bone which is now recognized as an important lesion occurring in the jaws and one which must be differentiated from neoplasms.

P. B.

Occupational Marks. By Francesco Ronchese, M.D., Boston Univ. School of Med.; Pp. 181; 163 Ills. New York: Grune & Stratton, 1948. Price, $5.50.

This brief volume is a tribute to its author. It emphasizes the place the objective dermatologic method of "look first and ask afterward" should have in the general scheme of medicine and specifically in personal identification. Dr. Ronchese has made a hobby "pay off" by producing within 181 pages a well-documented, excellently-illustrated compendium of occupational marks. While many of these data are available in scattered sources (adequately given in the bibliography), this is the most accessible compilation in English for the interested reader.

Included in this guide are certain general aspects of the subject such as specific occupational markings; professional markings; body areas and distinctive markings; deceptive markings and legal problems and classification of markings.

Although this volume is unique in many ways, its usefulness, in spite of the table of contents and index, could be enhanced by the addition of several lists with appropriate text and figure references, such as, for example, a list of marks and the particular occupations commonly yielding them, and a list of occupations with the marks produced by them.

H. B.

Take Off Your Mask. By Ludwig Eidelberg, M.D., New York Psychoanalytic Institute. Pp. 230. New York: International Universities Press, 1948. Price, $3.25.

This unusual book offers an account of psycho-analytic procedures to physicians and laymen. The author, a member of the Vienna, British and American Psychoanalytic Societies, has a remarkable ability to condense his stories and to make them interesting. His book of 8 chapters and 8 cases will richly repay its readers.

E. B.

Psychiatry. By William A. O'Connor, L.M.S.S.A. (Lond.). Pp. 380. Balt.: Williams & Wilkins, 1948. Price, $9.00.

In this "short treatise" based on hospital and teaching experience in England, the author gives clinical descriptions of the neuroses and psychoses which are eclectic and conventional. In general he favors a psychoanalytic explanation of pathology. But in the discussion of wide principles he goes far to the left as he apparently reacts against mechanistic ideas prevalent in Britain and comes near suggesting that the real origin of all illness is in the mind.

E. B.

Medullary Nailing of Küntscher. By Lorenz Böhner, MlD., Prof of Surgery, Tretter, M.D. Pp. 386; 1261 ills. Balt.: Williams & Wilkins, 1948. Price, $7.00. Univ. of Vienna. Translated by Hans

Intramedullary nailing for fractures of long bones, introduced by Küntscher of Germany in 1940, has been used extensively in Europe. Until now, however, the method has been rarely employed in the United States. A comprehensive critique of the method by Lorenz Böhler, a leading authority on fractures, is timely.

He analyzes experiences with intramedullary nailing in 600 fractures, emphasizing the narrow limits within which the method should be applied. Although he believes that intramedullary nailing is the best method available for the treatment of femoral shaft fractures which are not comminuted, he has discarded its use for the treatment of almost all fractures of the tibia, humerus, and forearm bones because of the frequency of complications.

Like most of Böhler's writing the book is didactic in tone. It could have been profitably shortened if similar details of technique had not been repeated for each bone. American surgeons will be surprised by the frequent neglect of the patient's general condition and the failure to use proper supportive treatment during operation. The illustrations are profuse and wisely selected. Instructions in the actual technique of nailing are detailed and lucid. Surgeons of this country are indebted to Böhler for furnishing this critical analysis of a valuable method of fracture treatment when experience here is as yet limited.

W. F.

Diagnosis in Daily Practice. By Benjamin V. White, M.D., Ass't Clinical Prof. of Medicine, Yale Univ., and Charles F. Geschickter, M.D., Prof. of Pathology, Georgetown Univ. Pp. 693; 360 ills. Phila.: J. B. Lippincott, 1947. Price, $15.00.

THIS book is not offered as a detailed textbook of medicine. It is intended as a guide for the advanced student, the intern, and the practitioner "In the selection of a daily routine which will embrace the more important and comprehensive diagnostic procedures" proven to be of value in the diagnosis of disease in its earliest stages.

The book is divided into 5 parts. The first of these (Chapters 1 to 3) defines the major human diseases as determined by morbidity and mortality statistical studies and gives the etiological classification and regional distribution of these diseases in the body. Lastly a routine diagnostic survey, utilizing procedures of known value in the diagnosis of the major diseases, is formulated. Part II (Chapters 4 to 12) is devoted to a discussion of the important symptoms occurring in the presence of the major diseases. Part III (Chapters 13 to 20) similarly deals with abnormal physical findings, and Part IV (Chapters 21 to 26) discusses laboratory procedures of use in diagnosing the major diseases. In each of these Parts are given differential diagnostic lists pertinent to the subject matter discussed therein. Part V (Chapters 27 to 49) presents the clinical features of the major diseases, with tables giving their differential diagnosis.

The authors can be commended for their practical and unique approach to an old and difficult problem. To this extent physicians will find this book of interest, but otherwise they are likely to find in it little that has not already been presented just as well or better elsewhere.

The publisher can be commended for presenting a book that is well bound and well printed on high quality paper. Illustrations, graphs, and tables are adequate and well done but there are a goodly number of typographical errors in the text. R. K.

HEMATOLOGY. By CYRUS C. STURGIS, M.D., Prof. of Internal Medicine, Univ. of Michigan Medical School. Pp. 915; 72 ills. Springfield, Ill.: Charles C Thomas, 1948. Price $12.50.

THIS volume, of imposing size and format, contains a good many typographical errors. Some of the colored plates are not informative. There is considerable redundancy of discussion. Some personal case reports might well have been omitted. A few strictly up-to-date topics, for whatever they may be worth, are missing from the index, such as: hypersplenism, hyperheparinemia, mast cells, the use of protamine and toluidin blue, "L.E." cells, cryoglobulins, auto-agglutinins, cold agglutinins, folic acid "antagonists", urethane, nitrogen mustard, "B-12", and "sludged blood".

Despite these adverse criticisms, the reviewer treasures this fine, scholarly clinician's summing up of his hematological wisdom in the 23 chapters of this worth while book. Particularly valuable are the splendid paragraphs of history which introduce each major topic. For these as well as for the generally excellent, wise, authoritative clinical discussions of all important hematological subjects, the book is cordially recommended to students, practitioners, and specialists in the field. Although space-consuming, the duplication of bibliographic references, at the bottom of the pages as well as at the end of the book, is an innovation which is helpful and useful.

T. F-H., Jr.

PATHOLOGY. Edited by W. A. D. ANDERSON, M.A., M.D., F.A.C.P., Professor of Pathology and Bacteriology, Marquette Univ. School of Medicine. Pp. 1453; 1183 ills., 10 color plates. St. Louis: C. V. Mosby, 1948. Price, $15.00.

THIS book is one of the most outstanding single texts on pathology which has been published in recent years. While the subjects of the chapters run the usual gamut of general and special pathology, often fine detail and recent research advances are included with the general information. The chapters are presented by different authors, many of them being leading investigators in their field, and consequently the text has more authority and fewer mistakes than most textbooks of pathology. The index is not complete, as occasional references are omitted. The book is replete with excellent illustrations. With the enormous amount of information contained within the 1400 odd pages, this text may be used with profit either for reference or for student teaching. I. Z.

THE PRACTICE OF ENDOCRINOLOGY. By RAYMOND GREENE, M.A., D.M., and 6 collaborators. Pp. 366; 53 ills. London: Eyre & Spottiswoode, 1948. Price, $10.60.

THIS book, planned for the general practitioner, essays to encompass the entire field of endocrinology in 10 chapters, with chief attention to diagnosis and treatment and little emphasis on physiology and pathology. As is usual, considerable variation in style and quality results from the collaborative effort. Though completed in 1946, the book's appearance was so delayed that a number of important recent advances are not included.

Some of the terminology will be a little strange to American readers. A number of subjects are either ignored completely or treated inadequately (e.g. hypogonadism in the male, ovarian deficiency with dwarfism, the relation of the parathyroids to renal disease, toxic nodular goiter, malignant tumors of the thyroid, the use of radioactive iodine). This book is not a major contribution to endocrinology, but may be a useful guide for the general practitioner. E. R.

ESSENTIALS OF PATHOLOGY. By LAWRENCE W. SMITH, M.D., and EDWIN S. GAULT, M.D., Temple Univ. School of Medicine. 3d ed. Pp. 764; 740 ills., many in color. Phila.: Blakiston, 1948. Price, $12.00.

IN this standard textbook, first published in 1938, the general method of presentation has not been changed but numerous improvements have been made. The text has been completely reset, revised, and augmented. Reduction of the page size and of the number of pages has made the book much lighter and easier to handle. Space has been saved by condensing the case histories and eliminating blank spaces intended for students' notes. The high quality of the illustrations has been maintained by the addition of 61 new figures. As a text for students it can be well recommended. W. S.

THE CLINICAL APPRENTICE: A GUIDE FOR STUDENTS OF MEDICINE. By JOHN M. NAISH, M.D., M.R.C.P., and JOHN APLEY, M.D., M.R.C.P., Bristol Univ. Pp. 200; 71 ills. Balt.: Williams & Wilkins, 1948. Price, $4.50.

Delightfully written in that inimitable English style, this small volume on physical examination and diagnosis should be required reading for all medical students. The material is succinctly and interestingly presented. The first section is concerned with the "leisurely examination", the second with the unconscious patient. Emphasis is placed upon the proper technics of examination. The book merits our unqualified approval. The price seems high and may restrict its widespread use. G. R.

EXPERIMENTAL IMMUNOCHEMISTRY. By ELVIN A. KABAT, Ph.D., Columbia Univ., and MANFRED M. MAYER, Ph.D., Johns Hopkins Univ., with a foreword by MICHAEL HEIDELBERGER. Pp. 567; 86 ills. Springfield, Ill.: Charles C Thomas, 1948. Price, $8.75.

INVESTIGATORS and technicians working in the fields of immunology, allergy, biochemistry, and medicolegal procedures will be well-served by this book on laboratory technics. The emphasis here is on the methods of quantitative measurements dealing with antigens and antibodies primarily. Relatively few theoretical considerations are presented unless they apply directly to the methods of measurement. Kabat and Mayer have utilized an extensive literature in the field to illustrate the handling of experimentally obtained results with tables and graphs of data. The text is well-written by authors who have had an extensive experience investigating immunochemical processes. Technics now in use for detecting Rh blood factors and antibodies have not been considered, but otherwise the scope of the book is broad and thorough. J. F.

THE CHILD IN HEALTH AND DISEASE. By CLIFFORD R. GRULEE, M.D., Rush. Prof. of Pediatrics, Univ. of Illinois, and R. CANNON ELEY, M.D., Harvard Univ. Pp. 1066; illustrated. Balt.: Williams & Wilkins, 1948. Price, $12.00.

THIS new textbook of pediatrics should immediately take a proper place in the forefront as one of the leading texts in the specialty. As is the trend nowadays with "complete" presentations, a large group of collaborating experts rather than a single author or pair of authors have been responsible for the subject matter. The almost innumerable subjects which come within the scope of pediatrics have been covered, including adolescence, surgical conditions, and growth and development; yet the allotments of space have been kept in proper proportion to the practical importance of the respective topics. The book can be recommended as an authoritative and up to date text, of special interest to students, practitioners, and also as a desk reference. I. W.

THE 1947 YEAR BOOK OF PATHOLOGY AND CLINICAL PATHOLOGY. Edited by HOWARD T. KARSNER, Prof. of Pathology, Western Reserve Univ., HERBERT Z. LUND, and ARTHUR HAWLEY SANFORD, Profs. of Clinical Pathology, Univ. of Minnesota. Pp. 558; 102 ills. Chicago: Year Book Publishers, 1948. Price, $3.75.

THE Year Book of Pathology was a war casualty, this being the first volume since 1941, with abstracts limited to articles published in 1947. In addition they have added valuable material by inviting leaders in a few active fields of research to submit concise reviews.

The book is divided into 2 major parts, general and special pathology 312 pages, and clinical pathology 224 pages. The articles to be abstracted were well chosen but not infrequently the abstracts fail to give a clear idea of the contents of the original article. Even so the main purpose of the book is accomplished if it calls the readers' attention to articles they may wish to read in the original. For this purpose it can be recommended. W. S.

NEW BOOKS

Hydrops congenitus universalis beim Kaninchen, eine erbliche fetale Erythroblastose. By HANS NACHTSHEIM und HANS KLEIN. Abhandl. d. deut. Akad. d. Wiss. zu Berlin. Pp. 71; 25 ills. Berlin: Akademie-Verlag, 1948. Price, 7.50 DM.

Cornel Conferences on Therapy. Vol. 3. Edited by HARRY GOLD, M.D., *et al.* Pp. 337. New York: The Macmillan Company, 1948. Price, $3.50

Annual Review of Microbiology. Vol. II. Edited by CHARLES E. CLIFTON, SIDNEY RAFFEL, Stanford Univ., and H. ALBERT BARKER, Univ. of California. Pp. 532. Stanford, Cal.: Annual Reviews, Inc., 1948. Price, $6.00.

This, the second of a useful series, contains articles on 18 subjects ranging from general topics such as bacterial metabolism to the more specific spirochetes, yeasts, and so on.

Dementia Praecox. By LEOPOLD BELLAK, M.D., Assoc. in Psychiatry, New York Medical College. Pp. 456. New York: Grune & Stratton, 1948. Price, $10.00.

This is an important book on an important subject. It is a comprehensive summary of the work done in the field from 1936-1946 (initial study by Dr. Nolan Lewis along the same lines was published in 1936).

W. P.

Medical Clinics of North America, Philadelphia Number, November 1948, *Recent Advances in Gynecology and Obstetrics.* Pp. 1483-1771. Phila.: W. B. Saunders, 1948. Price, $15.00 a year.

This volume gives the present-day views concerning a wide variety of frequently met problems, such as menstruation and menstrual disorders, management of the menopause, leukorrhea, ovarian cysts, the Rh factor, cancer detection and problems of pregnancy. In addition, it contains a useful 3-year index. This issue maintains the high standards of the series.

H. H.

The Frontal Lobes. Edited by JOHN F. FULTON, M.D., CHARLES D. ARING, M.D., and S. BERNARD WORTIS, M.D. Proc. of the Assoc. for Research in Nervous and Mental Disease. Vol. 28. Pp. 901; 237 ills. Balt.: Williams & Wilkins, 1948. Price, $12.50.

The 37 chapters of the 4 parts (Biology of the Frontal Lobes, Experimental Studies, Chemical Studies, Frontal Lobotomy) of this comprehensive report are aimed at "a critical evaluation of both the physiological basis of the lobotomy procedure and the clinical results which have so far been obtained."

Emergencies in Medical Practice Edited by A. ALLAN BIRCH, M.D., F.R.C.P., Chase Farm Hospital, England. Pp. 468; 113 ills., 8 in color. Balt.: Williams & Wilkins, 1948. Price, $7.00.

Psychiatry for the Millions. By BENZION LIBER, M.D., Prof. of Psychiatry. Pp. 307. New York: Frederick Fell, 1949. Price, $2.95.

Personality Projection in the Drawing of the Human Figure. By KAREN MACHOVER, Ph.D. Pp. 181. Illustrated. Springfield, Ill.: Charles C Thomas, 1949. Price, $3.50.

An outline of a method of personality analysis based on the interpretation of the subject's drawings of the human figure. The principles of such an analysis are surveyed in a tentative way, though "reasonably verified" through thousands of drawings correlated with their individual case records. To the casual reader interpretations often seem fantastically far fetched, though no more so than those applied to much of modern art.

An Introduction to Physics in Nursing. By HESSEL HOWARD FLITTER, R.N., M.A. Pp. 179; 99 figs. St. Louis: C. V. Mosby, 1948. Price, $3.25.

Adolescence Problems. By WILLIAM S. SADLER, M.D., F.A.P.A., Consulting Psychiatrist, Columbus Hospital, Chicago. Pp. 466. St. Louis: C. V. Mosby, 1948. Price, $4.75.

The experiences of a specialist in the field for more than 40 years offered as a help to physicians, parents and teachers.

Psychological Medicine. Modern Trend series. Edited by NOEL G. HARRIS, Civil Consultant in Psychological Medicine to the Royal Navy. Pp. 450. New York: P. B. Hoeber, 1948. Price, $10.00.

Of the 19 chapters, 17 are by British authors. Consideration of the differences from American procedure—numerous but seldom important—should be interesting and valuable to specialists in the field.

Recent Progress in Hormone Research. Proceedings of the Laurentian Hormone Conference. Edited by GREGORY PINCUS. Pp. 378. Illustrated. New York: Academic Press, 1949. Price, $7.80.

This Volume III contains 12 articles on 5 aspects of hormone research.

Anesthesia: Principles and Practice, a Presentation for the Nursing Profession. By ALICE M. HUNT. Pp. 148. New York: G. P. Putnam's Sons, 1949. Price, $2.60.

Hearing is Believing By MARIE HAYS HEINER. Introduction by RUPERT HUGHES. Pp. 126. Cleveland and New York: World Pub. Co., 1949. Price, $2.00.

A book written to help the hard of hearing and the deaf by one of them.

Proceedings of the New York Pathological Society. Edited by ANTONIO ROTTINO. Pp. 80. 1948. Price not given.

Medical Statistics from Graunt to Farr. By MAJOR GREENWOOD, D.Sc., Prof. Emeritus of Epidemiology and Vital Statistics, Univ. of London. Pp. 73. New York: The Macmillan Company, 1948. Price, $2.00.

THE 1941 and 1943 Fitzpatrick Lectures on the History of Medicine.

Elementary Anesthesia. By WILLIAM N. KEMP, M.D., Children's Hospital, Vancouver, Canada. Pp. 289; 100 ills. Balt.: Williams & Wilkins, 1948. Price, $5.00.

THERE may well be a need for a textbook designed for the "busy undergraduate,—and the busier practitioner", but such a book should be accurate and authoritative. This volume is neither. It is full of outdated theories, incorrect statements and poor advice. A few examples: on page 12 is copied an old diagram which confuses the carotid sinus with the carotid body; on the next page a statement "the respiratory center is *probably* situated in the pons and upper medulla," based on a 1923 reference and ignoring the recent work of Pitts;

a grossly inaccurate discussion of the dangers of excessive absorption of carbon dioxide by closed system methods of anesthesia. Coramine is recommended as the "one analeptic which far surpasses all others in effectiveness," a statement that would find but little support. The book cannot be recommended. R. D.

Studies in Analytical Psychology. By GERHARD ADLER, Ph.D., Fellow of the British Psychological Society. Pp. 250; 19 ills. New York: W. W. Norton, 1948. Price, $4.00.

THIS book is chiefly an exposition of the psychologic concepts of C. G. Jung. It contains 6 papers which describe such things as the differences between Jung's analytical psychology and Freud's psychoanalysis, methods of procedure, the conception of the collective unconscious and archetypes, the ego and the life-cycle, the point of view of analytic psychology to religion; and Jung's contribution to modern consciousness. The book will be of interest to people who are thoroughly familiar with the field of psychiatry as an exposition of certain controversial ideas, theories and techniques. Even if the school of thought which is presented does not meet with universal agreement, the book is worth reading. W. P.

The Management of Binocular Imbalance. By EMANUEL KRIMSKY, M.D., Adjunct Prof. of Ophthalmology, New York Polyclinic Medical School. Pp. 464; 200 ills. Phila.: Lea & Febiger, 1948. Price, $12.50.

THE author deals with such problems as: "1.) The meaning of binocular cooperation in all visual or accommodative ranges as well as for selective directions of gaze. 2.) The examination of binocular status in an objective or purposeful manner. 3.) When to interpret binocular coordination as normal or flexible . . . 4.) How binocular imbalance can affect visual function . . . 5.) The significance of symptomless . . . binocular imbalance. 6.) How to treat . . . when the eyes appear straight. 7.) When cross-eye is apparent, how shall we evaluate it from the standpoint of the need of possible . . . therapy? 8.) When shall we prescribe prisms? 9.) When shall we resort to medical or surgical treatment? 10.) What are the merits of binocular training?" (Author's preface.)

Psychiatry in General Practice. By MELVIN W. THORNER, M.D., D.Sc., Asst. Prof. of Neurology, Graduate School of Med., Univ. of Penna. Pp. 659. Phila.: W. B. Saunders, 1948. Price, $8.00.

THE author, believing that "most preventive psychiatry lies in the hands of the general practitioner", has written this book as "an attempt to lift psychiatry out of the realm of terra incognita for those whose primary efforts are spent in other fields." The book has good points, but suffers in comparison with "Teaching Psychotherapeutic medicine" (the excellent report of a joint effort sponsored by the Commonwealth Fund to teach practical psychiatry to general practitioners). Many case presentations are included which are often written in a short-story type of style. There appears to be more practical information in the section on methods than in other sections of the book. Some important subjects are inadequately discussed: for example, the importance of the doctor-patient relationship in therapy. The question of suicide, though mentioned in several case histories, is not considered adequately. (For comparison see: Maurice Levine "Psychotherapy in Medical Practice", Macmillan, 1942.) W. P.

The Commonsense Psychiatry of Dr. Adolf Meyer. Edited, with Biographic Narrative, by ALFRED LIEF. Pp. 677. New York: McGraw-Hill, 1948. Price, $6.50.

MR. LIEF, author of several biographies, has skillfully assembled and edited 52 reports, journal articles, and addresses of Dr. Adolf Meyer, the eminent psychiatrist. Biographical chapters are interspersed between some of the sections which contain Dr. Meyer's writings. The book is in no sense a text book of psychiatry. It is, rather, a presentation of the life, thoughts, speeches, writings, and philosophy of America's most outstanding psychiatrist. In view of the tremendous influence which he has had on psychiatry, and in view of the relative inaccessibility of most of his writings, this book is a valuable contribution. The whole medical profession, but especially that portion of it which is in the field of Psychiatry, owes a real debt of gratitude to Mr. Lief. W. P.

Pediatric Anesthesia. By M. DIGBY LEIGH, M.D., and M. KATHLEEN BELTON, M.D., Vancouver General Hospital, Canada. Pp. 240; 84 ills. New York: The Macmillan Company, 1948. Price, $5.50.

THIS is the first monograph to appear on this important subject. The foremost achievement of the authors is to indicate the wide variety of methods of anesthesia that can be used in children. To a reader familiar with pediatric anesthesia, the book may be a disappointment, as a relatively insignificant portion of the text concerns itself with discussions of the great number of perplexing problems of child anesthesia. Technic is emphasized almost to the exclusion of theory. However, considered as a book on technic, it will be a valuable addition to the library of the anesthetist who occasionally does pediatric anesthesia.

J. E.

Synopsis of Psychosomatic Diagnosis and Treatment. By FLANDERS DUNBAR, M.D., *et. al.* Pp. 501; 12 ills. St. Louis: C. V. Mosby, 1948. Price, $6.50.

THIS book will be of interest and practical use to general practitioners and students of medicine as well as to the specialist in the "functional" (emotional) aspects of disease. It is well organized and contains in summary form a reflection of the most important studies and findings in the field. It also includes a useful list of references.

W. P.

NEW EDITIONS

Diseases of the Ear, Nose, and Throat. By DOUGLAS G. CARRUTHERS, M.B., Ch.M. (Sydney), F.R.A.C.S. 2d ed. Pp. 344; 140 ills. Balt.: Williams & Wilkins, 1948. Price, $7.00.

A Synopsis of Physiology. By A RENDLE SHORT, Late Prof. of Surgery, Univ. of Bristol, C. L. G. PRATT, Fellow of Christ's College, Cambridge, and C. C. N. VASS, Reader in Physiology, Univ. of London. 4th ed. Pp. 346; 23 figs. Balt.: Williams & Wilkins, 1948. Price, $6.00.

Healthful Living. By HAROLD S. DIEHL, M.A., M.D., Sc.D., Prof. of Preventive Medicine and Public Health, and Dean of the Med-

ical Sciences, Univ. of Minnesota. 3d ed. Pp. 595; 46 figs. New York: Whittlesey House Health Series. McGraw-Hill, 1949. Price, $4.50.

"In this book he offers a simple guide on the subject of health for all who are interested in getting the most out of the body with which they began life, in avoiding the snares for the unwary, and in developing for the future a race of men and women capable of carrying on the tradition of healthfulness." (Dr. Fishbein's foreword.)

Introduction to Organic and Biological Chemistry. By L. EARLE ARNOW, Ph.D., M.D., and HENRY C. REITZ, Ph.D. 2d ed. Pp. 795; 90 ills. St. Louis: C. V. Mosby, 1949. Price, $5.75.

With the advances achieved in this field in the 6 years that have passed since the 1st edition, it is not surprising that a radical revision has had to be performed—whole new sections added, and changes and expansions of many others.

Common Skin Diseases. By A. C. ROXBURGH. 8th ed. Pp. 497; 212 ills., 8 in color. Phila.: Blakiston, 1948. Price, $7.00.

This text continues the good features of the earlier editions with much added new material, well documented usually by British references. The chapter on varicose veins, eczema and ulcer has been rewritten. A text with 8 editions in 16 years speaks for itself.

H. B.

NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

MANUSCRIPTS intended for publication in THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMBHAAR, School of Medicine, University of Pennsylvania, Philadelphia 4, Pa. Articles are accepted for publication in THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively, except in the case of subsequent publication in Society proceedings.

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